Review Article

Society of Family Planning committee consensus on Rh testing in early pregnancy☆☆☆

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A R T I C L E   I N F O

Article history:
Received 28 June 2022
Received in revised form 8 July 2022
Accepted 11 July 2022

Keywords:
Abortion
Early pregnancy loss
Fetomaternal hemorrhage
Rh immunization
Rh immunoglobulin
Rh sensitization

A B S T R A C T

Historical evidence that fetal red blood cell (RBC) exposure during early spontaneous or induced abortion can cause maternal Rh sensitization is limited. A close reading of these studies indicates that forgoing Rh immunoglobulin administration before 12 weeks gestation is highly unlikely to increase risk of Rh (D) antibody development, and recent studies indicate that fetal RBC exposure during aspiration abortion <12 weeks gestation is below the calculated threshold to cause maternal Rh sensitization, and the amount of fetomaternal hemorrhage during dilation and evacuation procedures up to 18 weeks gestation is adequately treated with 100 mcg of Rh immunoglobulin. We provide updated recommendations for Rh immunoglobulin administration based on this new evidence.

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1. Background

Rh-negative patients who are exposed to the Rh(D) antigen may become sensitized and immunized to Rh-positive red blood cells (RBCs)[1]. Production of Rh(D) antibodies in subsequent pregnancies can cross the placenta and destroy the RBCs of any Rh-positive fetus, leading to hemolytic disease of the newborn. The process of sensitization is multifactorial, dependent on volume of fetal red blood cell exposure, ABO compatibility and other factors [1]. Even prior to the discovery of Rh immunoglobulin, only 9% to 10% of pregnancies in Rh-negative patients led to sensitization.

Hemolytic disease of the newborn can generally be avoided, as giving Rh immunoglobulin at 28-weeks’ gestation and again at delivery has decreased the rates of immunization from 10% to 0.2% [2]. While administration of Rh immunoglobulin later in pregnancy is recommended, the gestational age at which this becomes necessary is not known. Conclusive evidence of benefit of Rh immunoglobulin administration in early pregnancy after spontaneous or induced abortion has not been found, as rates have not decreased further with routine administration of Rh immunoglobulin earlier in pregnancy [2].

The lack of evidence for use of Rh immunoglobulin in early pregnancy, coupled with improved techniques for measuring fetal RBCs, and better data collection have led to new research in this topic. Increased use of medication abortion [3], decreased use of sharp curettage, increased self-managed abortion [4,5], and updated FDA labeling removing the in-person dispensing requirement for mifepristone [6] illustrate changes in clinical care that have occurred over the past 2 to 3 decades. Evolving research and clinical practices warrant reconsidering early pregnancy Rh immunoglobulin administration recommendations which may add an unnecessary barrier to abortion care. This committee consensus statement recommends providing Rh immunoglobulin only after 12 weeks gestation for spontaneous abortion or medication or aspiration abortion.

☆ Conflict of interest: Sarah Horvath is a Nexplanon Trainer for Organon. The other authors report no conflicts. The Society of Family Planning receives no direct support from pharmaceutical companies or other industries for the development of clinical guidance.

☆☆ Funding: No specific funding was provided for the development of this document.

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https://doi.org/10.1016/j.contraception.2022.07.002
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2. Clinical questions

2.1. What is the existing evidence for Rh immunoglobulin administration after spontaneous or induced abortion?

Evidence to support or refute use of Rh immunoglobulin early in pregnancy is scant. In 1972, Visscher published the only randomized controlled trial prior to widespread adoption of Rh immunoglobulin administration [7]. Women undergoing spontaneous abortion at 8 to 24 weeks were randomized to receive Rh immunoglobulin or placebo (homologous gamma globulin). Twenty-five of the 29 patients receiving placebo underwent curettage for treatment of incomplete abortion, and none were sensitized by 6 months of follow-up. The six subsequent Rh-positive pregnancies within the placebo arm were all unaffected. Another cohort study, conducted before Rh immunoglobulin was routinely used in early pregnancy, looked at 32 Rh-negative patients having an Rh-positive live birth following a single spontaneous abortion [8]. They found only one case of sensitization in a patient who had curettage for incomplete abortion at 16 weeks. A Cochrane review included only the study by Visscher and concluded the data are insufficient to make a recommendation, and so defers to the guidelines of each country, which differ [9].

In the Netherlands, neither Rh testing nor treatment for Rh-negative status is performed before 7 weeks' gestation for induced abortion, nor before 10 weeks' gestation for spontaneous abortion. In Canada, Rh-negative patients are routinely given Rh immunoglobulin at any gestational age for any bleeding. A 2019 study using nationalized clinical databases for both countries included 3.8 million patients [10]. The researchers did not find clinically or statistically significantly higher Rh (D) antibodies in the Dutch population, 4.03 (95% CI: 3.93 – 4.12) per 1000 pregnant women compared with 4.21 (95% CI: 4.12 – 4.30) per 1000 pregnant women in Canada, despite differences in Rh immunoglobulin administration guidelines.

Referencing existing literature, a recent study calculated that 250 fetal RBCs per 10 million adult RBCs is a conservative threshold concentration of fetal RBCs necessary to cause maternal sensitization [11]. This fetal RBC concentration is much lower than would be detectable by Kleihauer-Betke (K-B), the traditional technique for detecting fetal RBCs in maternal blood, which has a lower limit of detection of 4000 fetal RBCs per 10 million adult RBCs. Flow cytometry is more sensitive and specific, with lower interobserver variability, than K-B. Flow cytometry was used to analyze serum samples for 37 patients before and after uterine aspiration up to 12 weeks gestation. The level of fetal RBCs did not cross the estimated sensitization threshold in any samples.

Hsia et al. used K-B testing to determine the quantity of fetomaternal hemorrhage among 300 patients undergoing dilation and evacuation from 15 to 23.6 weeks gestation [12]. None of the 24 patients less than 16 weeks had fetomaternal hemorrhage greater than 5mL and none of 64 patients at less than 18 weeks gestation had fetomaternal hemorrhage greater than 10mL. The remaining patients were all above 18 weeks gestation and should continue to receive the traditional 300mcg dose.

Hollenbach et al. used flow cytometry to assess fetal RBCs in 100 patients at 6 to 22 weeks (mean 17 weeks and 4 days) undergoing uterine evacuation and found that 69% had fetal RBCs present in maternal circulation prior to the procedure. Most of the patients with detectable fetal RBCs post-procedure also had them preprocedure, with only 14% exhibiting fetal RBCs for the first time post-procedure [13]. Although the sensitivity of the flow cytometry assay used in this study was similar to that of K-B (4.3 fetal RBCs/10,000 maternal RBCs), the individual percent changes in fetal RBCs pre and postprocedure were small and unlikely to be of clinical significance.

Altogether, recent evidence suggests that forgoing Rh immunoglobulin administration before 12 weeks gestation does not increase the risk of Rh (D) antibody development, fetal RBC exposure during aspiration abortion less than 12 weeks gestation is below the calculated threshold to cause maternal Rh sensitization, and the majority of abortion patients have detectable fetal RBCs even before the procedure with uncertain clinical relevance. These results call into question the clinical utility of routine Rh immunoglobulin administration in early pregnancy. Additionally, the amount of fetomaternal hemorrhage during dilatation and evacuation procedures up to 18 weeks gestation is adequately treated with 100mcg of Rh immunoglobulin (see dosing below).

2.1.1. What is Rh immunoglobulin and how is it made? What are the types and doses of Rh immunoglobulin?

Rh immunoglobulin is an antibody derived from pooled human plasma extracted from Rh-negative individuals who were born male and have been immunized to the Rho(D)-antigen through exposure to Rh-positive blood [14]. The mechanism of action of Rh immunoglobulin in Rh-negative pregnant individuals is not completely understood, but is dose dependent, with optimal Rh immunoglobulin dosing occurring as close as possible to exposure. Initial studies used a 72-hour window due to a study design that did not include weekend visits, however some efficacy is believed to continue even weeks after the bleeding event [15]. Nonpooled extract is not effective and synthetic Rh immunoglobulin is not clinically available.

Rh immunoglobulin is commercially available in a range of doses from different pharmaceutical manufacturers both within the United States and internationally. Within the United States, doses of 50 mcg (250 international units (IU)) and 300 mcg (1500IU) are available. In some countries, a 100mcg (500IU) dose is also available. Dosing strategies often include use of the 50mcg dose in the first trimester for estimated fetal whole blood hemorrhage into maternal circulation of 5 mL, with larger doses (100 mcg for 10 mL and 300 mcg for 30 mL of estimated hemorrhage of fetal whole blood [12]) used throughout the second and third trimesters. Although available evidence does not support routine use of Rh immunoglobulin in early pregnancy, if it is provided, fetal RBC exposure in the first trimester can reliably be treated with a 50mcg dose of Rh immunoglobulin. Controversy exists, however, over the necessary dose of Rh immunoglobulin at advancing gestational ages, and which other indications for qualifying or quantifying exposure throughout pregnancy should be considered. Whenever the indicated dose is unavailable, a larger dose may be substituted.

Detection of passive anti-D after administration of Rh immunoglobulin is dose dependent. To maintain passively acquired anti-D levels after repeated events which may lead to fetomaternal hemorrhage and sensitization, we recommend a dosing interval corresponding to Rh immunoglobulin dose volume: per event for 50 mcg, 6 weeks for 100 mcg, and 12 weeks for 300 mcg [16].

2.2. What are the costs associated with Rh testing and administration of Rh immunoglobulin?

Nearly six million pregnancies occur in the United States annually and about 48% of them have some first-trimester bleeding due to induced, spontaneous, or threatened abortion. Although only approximately 15% of the US population is Rh negative, most pregnant patients with bleeding in early pregnancy currently undergo assessment of Rh status. In 2022 dollars, the cost of running a type and screen was $92 – $123 [17]. For those receiving treatment, the cost of Rh immunoglobulin is either paid in full or subsidized by insurance, paid out-of-pocket by the patient, or amortized across
Table 1

<table>
<thead>
<tr>
<th>Organization(s)</th>
<th>Document</th>
<th>Year</th>
<th>Gestational Age</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACOG, SFP**</td>
<td>Practice Bulletin 225: Medication Abortion Up to 70 Days’ Gestation [23]</td>
<td>2020</td>
<td>≤ 70 d</td>
<td>Rh testing is recommended in patients with unknown Rh status before medication abortion, and Rh immunoglobulin should be administered if indicated. In situations where Rh testing and Rh immunoglobulin administration are not available or would significantly delay medication abortion, shared decision making is recommended so that patients can make an informed choice about their care. (Level C)</td>
</tr>
<tr>
<td>NAF</td>
<td>Forgoing Rh testing and anti-D immunoglobulin for women presenting for early abortion: a recommendation from the National Abortion Federation’s Clinical Policies Committee [19]</td>
<td>2022</td>
<td>&lt; 12 wk</td>
<td>It is reasonable to forgo Rh testing and immunoglobulin for women having any type of induced abortion before 12 wk from the last menstrual period.</td>
</tr>
<tr>
<td>WHO</td>
<td>Abortion care guideline [22]</td>
<td>2022</td>
<td>&lt;12 wk</td>
<td>For both medical and surgical abortion at &lt;12 wk: Recommend against Rh immunoglobulin administration</td>
</tr>
<tr>
<td>RCOG</td>
<td>Best practice in comprehensive abortion care [24]</td>
<td>2022</td>
<td>&gt;12 wk</td>
<td>• A determination of Rhesus blood status may be considered if the duration of pregnancy is over 12 wk and anti-D is available. • A determination of Rhesus blood status may be considered if the duration of pregnancy is over 12 wk and anti-D is available.</td>
</tr>
<tr>
<td>NICE</td>
<td>Abortion care [20]</td>
<td>2019</td>
<td>N/A</td>
<td>Providers should ensure that:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Rh status testing and Rh immunoglobulin supply does not cause any delays to women having an abortion • Rh immunoglobulin is available at the time of the abortion</td>
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<tr>
<td></td>
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<td>&gt; 70 d</td>
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<td>≤70 d</td>
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<tr>
<td>PPFA</td>
<td>PPFA Medical Standards and Guidelines - Interim Guidance, 2020 [Personal communication 02/22/2022]</td>
<td>2020</td>
<td>≤77 d</td>
<td>[No] requirement for Rh testing and Rh immunoglobulin administration for both medication and surgical abortion ≤77 d gestational age</td>
</tr>
</tbody>
</table>

* Edited for consistency of language
** The recommendations regarding Rh testing and administration from Practice Bulletin 225 are included here for reference. However, the guidance in this committee consensus serves to update the Society of Family Planning’s recommendations on Rh testing and administration.

all patients. The wholesale cost per 300mcg dose in the US is approximately $80, though the cost to the patient or insurer may differ, and typically is billed with an injection fee.

The monetary costs of Rh testing and treatment do not include the costs of follow up, which can be substantial, as clinicians must have processes in place for tracking Rh test results, informing patients of Rh-negative results, and ensuring Rh immunoglobulin administration. Consequently, with routine Rh screening protocols, some patients must await results in an emergency room or other clinical setting, adding costs to the patient and/or health care system. Patients relying on telemedicine or traveling far for abortion or pregnancy loss care who are advised to receive Rh immunoglobulin may also incur the logistical and financial burdens of finding a local clinical setting for Rh testing and administration, as well as the potential burdens associated with stigma and undesired disclosure.

Although the smaller 50mcg dose is considered sufficient to prevent sensitization in early pregnancy, many health systems universally administer the 300mcg dose. This overuse in wealthy countries has global consequences for resource-poor settings, where Rh immunoglobulin may be unavailable. Global shortages have occurred in the past. Additionally, Rh immunoglobulin is a human blood product, dependent on donors and subject to those attendant risks. The current supply is screened for known pathogens and very safe. However, a new bloodborne pathogen may not be immediately detectable in the future.

2.3. What are the existing recommendations for Rh immunoglobulin administration?

The 2013 Cochrane review assessing the effects of Rh immunoglobulin administration among patients undergoing spontaneous abortion (miscarriage) between 8 to 24 weeks gestation concluded that there is “Insufficient data to evaluate the practice of anti-D administration in an unsensitised Rh-negative mother after spontaneous miscarriage... and should be based on standard prac-
tice guidelines of each country” [9]. Similarly, a 2015 Cochrane review assessing the effects of Rh immunoglobulin throughout pregnancy also stated: “Existing studies do not provide conclusive evidence that the use of anti-D during pregnancy benefits either mother or baby in terms of incidence of Rhesus D alloimmunisation during the pregnancy or postpartum, or the incidence of neonatal morbidity” [18].

Since 2018, new evidence has led to changes in existing guidelines at many organizations. The National Abortion Federation (NAF) in the United States does not recommend Rh testing prior to 12 weeks gestation and recommends foregoing treatment for Rh negative patients undergoing procedural or medication abortion prior to 12 weeks [19]. The UK-based National Institute for Health and Care Excellence (NICE) advises against Rh testing for medication abortion prior to 10 weeks and consideration of foregoing testing for procedural abortion prior to 10 weeks [20]. Although the American College of Obstetricians and Gynecologists (ACOG) still recommends giving a 50mcg dose in early pregnancy loss, they changed their recommendation from “should receive” to “should be considered” in their 2018 interim update [21]. The WHO released new guidelines in March 2022 recommending against anti-D immunoglobulin administration <12 weeks for either medical or surgical abortion [22].

Tables 1 and 2 show the heterogeneity of recommendations in different countries. This means that vastly different standards are followed depending on geography, even when the populations of those countries have similar rates of Rh-negative blood type.

### 3. Conclusion

Emerging evidence and improved techniques with greater sensitivity and specificity to quantify fetal RBCs in maternal blood after abortion indicate that the risk of maternal Rh isoimmunization before 12 weeks gestation among patients undergoing spontaneous, medication, or uterine aspiration abortion is minimal. The costs associated with routine Rh screening and testing and Rh immunoglobulin administration of pregnant patients before 12 weeks gestation likely outweigh the benefits, especially as clinical abortion practices are evolving. The following recommendations are more consistent with international recommendations and the currently available evidence for Rh sensitization in the first two trimesters of pregnancy. We anticipate that these guidelines will need to be updated as new evidence is discovered. Given the consequences of undertreatment, these recommendations are purposefully conservative and will be updated as needed.

### 4. Recommendations

These recommendations are specific to spontaneous and induced abortion care occurring in the first two trimesters of pregnancy:

- If the fetus is reasonably certain to be Rh negative, Rhogam is not needed in any circumstance or any gestational age.
- Rh testing and administration are not recommended prior to 12 weeks gestation for patients undergoing spontaneous, medication, or uterine aspiration abortion (See summary Table 3)
- Uterine aspiration is the standard of care for uterine evacuation and sharp curettage is not recommended. However, if sharp curettage is deemed clinically necessary, it is unclear how this might impact the need for Rh immunoglobulin.
- For patients under 12 weeks gestation, although not recommended, Rh testing and Rh immunoglobulin administration may be considered at patient request as part of a shared decision-making process, discussing the patient’s future fertility desires in the context of existing data.
- Similarly, patients may decline recommended Rh immunoglobulin testing and administration. Common reasons for declining include, but are not limited to, no desire for future pregnancy, relative certainty that patient is Rh-positive, relative certainty that pregnancy is Rh-negative, and desire to avoid administration of human blood product. It is important to document the counseling, recommendation, and declination.
- Whenever administration occurs prior to 12 weeks gestation, a 50mcg (250 IU) dose of Rh immunoglobulin should be used.
- The 100mcg dose (500IU) of Rh immunoglobulin is recommended as safe and effective at 12-18 weeks gestation. This dose may be available in international settings or can be achieved by administering two-50mcg (250IU) doses.
- Continued administration of the 300mcg (1500IU) dose for patients undergoing abortion above 18 weeks gestation is prudent.
5. Future considerations

Ongoing clinical studies are underway to investigate fetal RBC concentration after abortion through 10 weeks among larger populations. We recommend that similar studies be undertaken for patients throughout the first and second trimesters. As evidence regarding Rh sensitization in early pregnancy accumulates, systematic reviews by indication should occur. As clinics adopt these new guidelines, longitudinal cohort studies should be undertaken to evaluate their uptake and efficacy.

Acknowledgments

This Committee Consensus was prepared by Sarah Horvath, MD, MSHP, Vinita Goyal, MD MPH, Sarah Traxler, MD, MSHP, Sarah Prager, MD, MAS and was reviewed and approved by the Clinical Affairs Committee on behalf of the Board of Directors of the Society of Family Planning.

References