Is it time to reconsider Rh testing and Rh D immune globulin treatment for miscarriage and abortion care in early pregnancy?

New guidelines propose to reduce the use of Rh testing and Rh D immune globulin administration for miscarriage and abortion care in early pregnancy

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All obstetrician-gynecologists know that pregnant patients who are Rh negative and exposed to a sufficient quantity of fetal red blood cells expressing Rh D antigen may become sensitized, producing Rh D antibodies that adversely impact future pregnancies with an Rh D-positive fetus, potentially causing hemolytic disease of the fetus and newborn. In countries where Rh D immune globulin is available, there is a consensus recommendation to administer Rh D immune globulin to Rh-negative pregnant patients at approximately 28 weeks' gestation and at birth in order to decrease the risk of alloimmunization and hemolytic disease of the fetus and newborn in future pregnancies.[1] In contrast to this global consensus, there is no worldwide agreement about how to manage Rh testing and Rh D immune globulin administration in cases of early pregnancy loss or abortion care before 12 weeks' gestation. This editorial examines the evolving guidelines of major professional societies.

The author reports no conflict of interest related to this article.

doi: 10.12788/obgm.0249

Guidelines consistent with the routine use of Rh D immune globulin in all cases of early pregnancy loss and abortion care

As of the publication date of this editorial, the **American College of Obstetricians and Gynecologists** (ACOG) Practice Bulletin on prevention of Rh D alloimmunization provides the following guidance based on consensus and expert opinion[2]:

- "Although the risk of alloimmunization is low, the consequences can be significant, and administration of Rh D immune globulin should be considered in cases of spontaneous first trimester miscarriage, especially those that are later in the first trimester."
- "Because of the higher risk of alloimmunization, Rh D-negative women who have instrumentation for their miscarriage should receive Rh D immune globulin prophylaxis."
- "Rh D immune globulin should be given to Rh D-negative women who have pregnancy termination either medical or surgical."

The Society of Obstetricians and Gynaecologists of Canada (SOGC) recommends that, "After miscarriage or threatened abortion or induced abortion during the first 12 weeks of gestation, non-sensitized D-negative women should be given a minimum anti-D of 120 µg."[3]

The liberal use of Rh D immune globulin in all cases of early pregnancy loss and abortion care is based, in part, on the following considerations:

1. the recognized safety of Rh D immune globulin administration[2,3]
2. the report that fetal megaloblasts may express Rh antigen as early as 38 days of gestation[4]

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3. the observation that 0.1 mL of Rh D-positive red cells may provoke an immune response in some Rh D-negative patients[5-7]
4. the estimate that in some patients with threatened miscarriage a significant quantity of fetal blood may enter the maternal circulation.[8]

Guidelines that suggest restricted use of Rh D immune globulin before 7 to 8 weeks' gestation

The **Reproductive Care Program of Nova Scotia** guideline from 2022 notes that "the benefits of administering Rh immune globulin before 8 weeks gestation have not been demonstrated." Given the burden of Rh testing and Rh D immune globulin administration they suggest that clinicians may withhold Rh testing and Rh D immune globulin administration in cases less than 8 weeks' gestation (less than 56 days) for spontaneous, threatened, or medication abortions if there is reliable pregnancy dating.[9]

The **Dutch Association of Abortion Specialists** guidelines from 2018 suggest to not provide Rh D immune globulin treatment in the following clinical situations: patients under 10 weeks' gestation with spontaneous miscarriage or patients under 7 weeks' gestation having an induced abortion.[10]

Guidelines that suggest restricted use of Rh D immune globulin before 10 to 12 weeks' gestation

There are a growing number of guidelines that recommend restricting the use of Rh testing and Rh D immune globulin treatment in the management of early miscarriage and induced abortion. In 2019, the United Kingdom's **National Institute for Health and Care Excellence** (NICE) recommended that for patients having a spontaneous miscarriage, Rh testing and Rh D immune globulin are not necessary before 10 weeks 0 days of gestation.[11] In addition, NICE recommends, "Do not offer anti-D prophylaxis to women who are having a medical abortion up to and including 10+0 weeks' gestation.…Consider anti-D prophylaxis for women who are rhesus D negative and are having a surgical abortion up to and including 10+0 weeks' gestation."[11]

In 2019, the **National Abortion Federation** (NAF) Clinical Policies Committee recommended that "…it is reasonable to forgo Rh testing and anti-D immunoglobulin for women having any type of induced abortion before 8 weeks from the last menstrual period. Prior to 8 weeks, the likelihood of fetal-maternal hemorrhage adequate to cause sensitization is negligible. Given that medication abortion is more similar to spontaneous abortion with less risk of fetal-maternal hemorrhage, forgoing Rh testing and anti-D immunoglobulin for medication abortion under 10 weeks may be considered."[12] In 2022, NAF noted, "Emerging epidemiologic and clinical evidence indicates that the risk of maternal-fetal hemorrhage caused by early abortion is negligible and Rh testing and provision of Rh immune globulin may not be necessary. It is reasonable to forego Rh testing and anti-D immunoglobulin for people having any type of abortion before 56 days and medication abortion before 70 days since the last menstrual period. The pregnancy dating at which people need Rh testing and anti-D immunoglobulin is not well established. Foregoing Rh testing and anti-D immunoglobulin for those using medication abortion through 11 to 12 weeks may be considered."[13]

In 2020 the **International Federation of Gynaecology and Obstetrics** (FIGO) Committee for Safe Motherhood and Newborn Health recommended, "The risk for sensitization is most probably extremely low for spontaneous abortions before 10 gestational weeks; however, data are scarce. Based on the clinical expertise of the guideline committee from the UK's National Institute for Health and Care Excellence (NICE), it is suggested that prophylaxis should be given only to women who are having a spontaneous abortion or medical management of miscarriage after 10 and 0/7 gestational weeks. Moreover, for women who have surgical management, prophylaxis may also be considered before 10 gestational weeks."[14]

In 2022 the **Royal College of Obstetricians and Gynaecologists** recommended that for induced abortion, medication or surgical, "a determination of Rhesus blood status may be considered if the duration of pregnancy is over 12 weeks and anti-D is available."[15] "If available, anti-D should be offered to non-sensitised RhD-negative individuals from 12 weeks of pregnancy and provided within 72 hours of the abortion."[15]

In 2022, the **Society of Family Planning** recommended that "Rh testing and administration are not recommended prior to 12 weeks gestation for patients undergoing spontaneous, medication or uterine aspiration abortion." "For patients under 12 weeks gestation, although not recommended, Rh testing and Rh D immune globulin administration may be considered at patient request as part of a shared decision making process."[16]

In 2022, the **World Health Organization** (WHO) reported "There are few studies examining Rh isoimmunization in unsensitized Rh-negative individuals seeking abortion before 12 weeks of gestation." "The evidence on the effectiveness of the intervention may favor the intervention, because fewer women in the intervention group (anti-D administration) had antibody formation after the initial pregnancy compared to women in the comparison group (no anti-D) and no harms (undesirable effects) of the intervention were noted."[17] The evidence referenced for these statements are two low-quality studies from 1972.[18,19] The WHO continues, "…after consideration of the resources required, cost-effectiveness and feasibility of administering anti-D, as well as the very low certainty of evidence on effectiveness, the expert panel concluded that overall, the evidence does not favor the intervention and decided to recommend against it for gestational ages < 12 weeks, rather than < 9 weeks, as mentioned in the 2012 guidance."[17] In conclusion, the WHO recommended that "for both medical and surgical abortion at < 12 weeks: Recommend against anti-D immunoglobulin administration."[17]

Guidelines that recommend restricted use of Rh D immune globulin during the first trimester, are based, in part, on the following considerations:

- there are no high-quality clinical trials demonstrating the benefit of Rh D immune globulin treatment in first trimester miscarriage and abortion care
- the Kleihauer-Betke technique cannot distinguish between maternal red blood cells expressing fetal hemoglobin (maternal F cells) and fetal cells, which has resulted in the over-estimation of the number of fetal cells in the maternal circulation[20]
- using a dual-label flow cytometry method that distinguishes maternal F cells and fetal red blood cells, maternal F cells usually far outnumber fetal red blood cells in the maternal circulation in the first trimester[20]
- among women in the first trimester undergoing uterine aspiration, the number of fetal cells in the maternal circulation is very low both before and after the procedure[20]
- Rh testing and Rh immune globulin administration is burdensome and expensive.[16]

Implications for your practice

The fundamental reason for the proliferation of divergent guidelines is that there is no evidence from high-quality randomized clinical trials demonstrating that Rh testing and Rh D immune globulin treatment in early pregnancy miscarriage or induced abortion care reduces the risk of hemolytic disease of the fetus and newborn. The Cochrane review on Rh D immune globulin administration for preventing alloimmunization among patients with spontaneous miscarriage concluded, "There are insufficient data available to evaluate the practice of anti-D administration in an unsensitized Rh-negative mother after spontaneous miscarriage."[21]

Given divergent guidelines, obstetrician-gynecologists must decide on which guideline to use in their practice. Clinicians may conclude that absent high-quality evidence from clinical trials, they will continue to use the ACOG/SOGC guidelines[2,3] in their practice, providing universal Rh testing and Rh D immune globulin treatment for all miscarriages and abortions, regardless of the gestational age. Other clinicians may conclude that Rh testing and Rh D immune globulin is not warranted before 8 to 12 weeks' gestation, because the number of fetal red blood cells in the maternal circulation in cases of miscarriage and induced abortion is too low in early pregnancy to induce a maternal immune response.[22] Based on recent studies demonstrating a low number of fetal red blood cells in the maternal circulation in the first trimester, family planning specialists are reducing the use of Rh testing and Rh immune globulin administration in both early pregnancy medication abortion and uterine aspiration abortion.[16] With regard to Rh testing and Rh D immune globulin treatment, the future will definitely be different than the past. It is likely that many clinicians will reduce the use of Rh testing and Rh D immune globulin treatment in patients with miscarriage or induced abortion in early pregnancy. ●

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