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 dilation 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 72hour 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