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Induced Abortion and the Risk of Rh Sensitization

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IMPORTANCE While population-level data suggest Rh immunoglobulin is unnecessary before 12 weeks' gestation, clinical evidence is limited. Thus, guidelines vary, creating confusion surrounding risks and benefits of Rh testing and treatment. As abortion care in traditional clinical settings becomes harder to access, many people are choosing to self-manage and need to know if ancillary blood type testing is necessary.

OBJECTIVE To determine how frequently maternal exposure to fetal red blood cells (fRBCs) exceeds the most conservative published threshold for Rh sensitization in induced first-trimester abortion.

DESIGN, SETTING, AND PARTICIPANTS Multicenter, observational, prospective cohort study using high-throughput flow cytometry to detect circulating fRBCs in paired maternal blood samples before and after induced first-trimester abortion (medication or procedural). Individuals undergoing induced first-trimester abortion before 12 weeks 0 days' gestation were included. Paired blood samples were available from 506 participants who underwent either medical (n = 319 [63.0%]) or procedural (n = 187 [37.0%]) abortion.

EXPOSURE Induced first-trimester abortion.

MAIN OUTCOMES AND MEASURES The primary outcome was the proportion of participants with fRBC counts above the sensitization threshold (125 fRBCs/5 million total RBCs) after induced first-trimester abortion.

RESULTS Among the 506 participants, the mean (SD) age was 27.4 (5.5) years, 313 (61.9%) were Black, and 123 (24.3%) were White. Three of the 506 participants had elevated fRBC counts at baseline; 1 of these patients had an elevated fRBC count following the abortion (0.2% [95% CI, 0%-0.93%]). No other participants had elevated fRBC counts above the sensitization threshold after induced first-trimester abortion. The median change from baseline was 0 fRBCs, with upper 95th and 99th percentiles of 24 and 35.6 fRBCs, respectively. Although there was a strong association between the preabortion and postabortion fRBC counts, no other baseline characteristic was significantly associated with postabortion fRBC count.

CONCLUSIONS AND RELEVANCE Induced first-trimester abortion is not a risk factor for Rh sensitization, indicating that Rh testing and treatment are unnecessary before 12 weeks' gestation. This evidence may be used to inform international guidelines for Rh immunoglobulin administration following first-trimester induced abortion.

Supplemental content

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Rh immunoglobulin is a finite human blood product used to prevent sensitization to the Rh antigen when patients negative for Rh are exposed to significant volumes of Rh-positive blood. Prior to the discovery of Rh immunoglobulin, 9% to 10% of patients negative for Rh became sensitized with each full-term pregnancy.[1] The maternal Rh sensitization rate decreased to between 1.1% and 1.6% with adoption of routine treatment at delivery and decreased further to approximately 0.2% with additional prophylaxis in the third trimester in the US, Canada, the UK, Europe, Australia, and New Zealand; however, no further reduction in incidence was seen in countries that adopted Rh immunoglobulin for bleeding events in early pregnancy.[2] Evidence to inform administration following induced first-trimester abortion is lacking. Overuse of Rh immunoglobulin by high-resource countries in settings without proven benefit, such as early pregnancy, increases cost and restricts the availability of its use in lower-resourced countries. These concerns have prompted revisiting these guidelines and knowledge gaps.[3,4]

In 2022, the World Health Organization recommended forgoing Rh testing and treatment prior to medication or procedural abortion at less than 12 weeks' gestation.[5] Although many professional guidelines have also shifted, substantial variability remains in recommendations for Rh testing and treatment in early pregnancy, both within and between countries.[5-8] For some clinicians, first-trimester Rh testing and treatment are deeply ingrained, and efforts to align recommendations may be facilitated by additional clinical evidence.[7-9] A 2013 Cochrane review concluded that there were "insufficient data to evaluate the practice of anti-D administration in an unsensitized Rh-negative mother after spontaneous miscarriage."[4] Clinical data using contemporary red blood cell (RBC) detection techniques to inform evidence-based practice are limited.[4] Early laboratory techniques lacked the specificity and precision necessary for evaluating low levels of exposure to fetal RBCs (fRBCs) near the threshold, as had been hypothesized at the time to occur in the first trimester. This study aimed to fill the knowledge gap using technologies unavailable at the time Rh immunoglobulin was discovered.

A previous pilot cohort study of participants undergoing procedures for spontaneous or induced abortion up to 12 weeks' gestation estimated the threshold of fRBCs proposed to cause sensitization in a minority of patients, and showed reliable detection of fRBCs at levels well below that threshold using refined flow cytometry protocols.[10,11] This study tested the hypothesis that fRBCs in the circulation of individuals undergoing induced procedural or medication abortion at less than 12 weeks' gestation are below the sensitization threshold.

Key Points

Question Is administration of Rh immunoglobulin necessary for individuals undergoing induced first-trimester abortion care?

Findings In this prospective study, 505/506 participants (99.8%) undergoing induced first-trimester abortion care had postprocedure fetal red blood cell counts below the published threshold for Rh sensitization. Three participants exceeded the threshold at baseline; no additional participants crossed this threshold after induced abortion.

Meaning Rh testing or immunoglobulin administration following induced first-trimester abortion is unnecessary.

Methods

Prospective Cohort

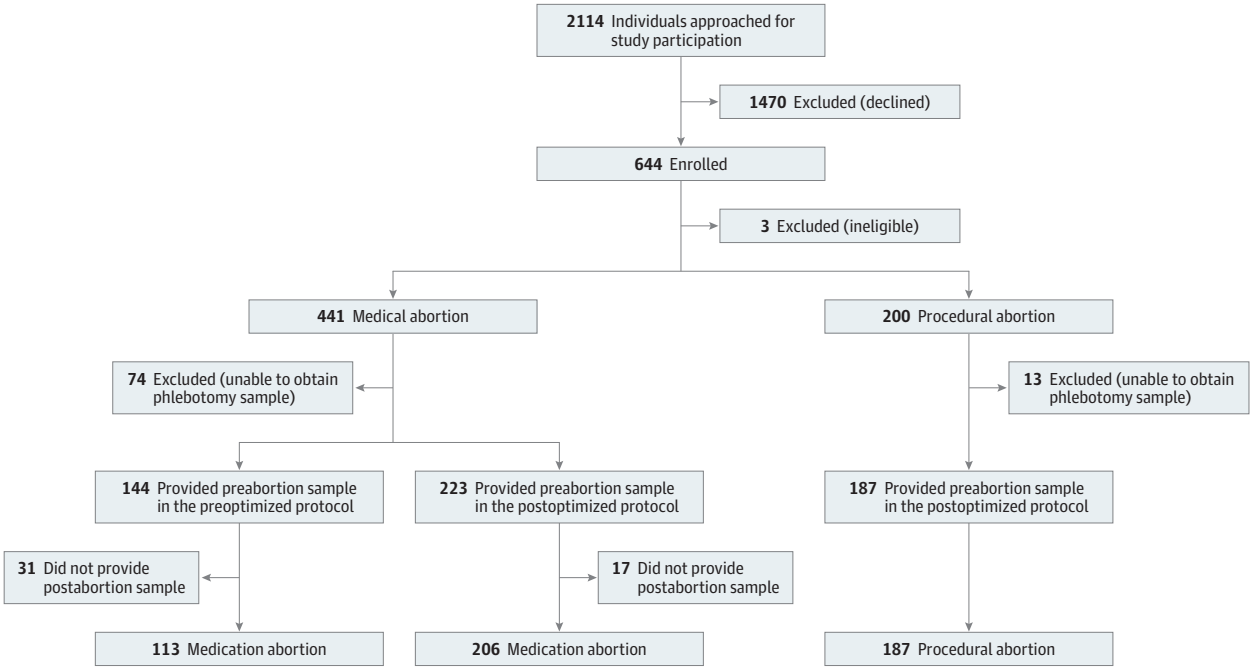
This study was approved by the institutional review board at the University of Pennsylvania. We approached all patients undergoing medication abortion at less than 12 weeks' gestation (**Figure 1**) at 4 clinical sites: University of Pennsylvania, Philadelphia Women's Center, Delaware County Women's Center, and Planned Parenthood League of Massachusetts, and written patient consent was obtained. Subsequently, we expanded eligibility criteria to include procedural abortion to improve generalizability of results and respond to constraints of the COVID-19 public health emergency. Information on race and ethnicity was self-reported and chosen from fixed categories; American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, and other categories were collapsed into an "other" category due to small numbers in each.

Exclusion criteria included sickle cell disease, β-thalassemia, hereditary persistence of fetal hemoglobin or other hemoglobinopathy, or being unwilling to participate in follow-up. Research team members extracted blood type and Rh status from the medical record and collected patient-reported survey data including demographics, medical and pregnancy histories, and bleeding history in the current pregnancy. We also recruited 6 participants to take part in a longitudinal substudy of the natural history of fRBC clearance from maternal circulation. These patients had blood drawn before abortion and after abortion at 1, 2, 4, 8, 12, 24, 48, and 72 hours. Because variability was not noted, no additional participants were enrolled for this substudy. The flow cytometry protocol was refined during the study, prior to inclusion of participants undergoing procedural management. Laboratory details, including cell fixation, permeabilization, 2-color panel staining, and data acquisition, are included in eMethods in Supplement 1. We also describe the optimization of these assays for larger sample sizes (5 million events) and adoption of the flow cytometry protocol for use on cryopreserved RBCs. Further, we created an exploratory 11-color flow cytometry panel for more refined gating and rare event detection and provided gating schema for the 2-color (eFigure 1 in Supplement 1) and 11-color (eFigure 2 and eTable 1 in Supplement 1) panels.

Primary Outcome Measure

Our primary outcome was the number of participants whose fRBC counts crossed the sensitization threshold of 125 fRBCs/5 million total RBCs.[10] Secondary outcomes included differences in fRBC counts before vs after abortion care, and differences in fRBC counts by gestational age and other maternal characteristics. For the time series substudy, we also assessed the natural history of clearance of fRBCs from the maternal circulation.

Figure 1. Patient Recruitment in Study of First-Trimester Abortion



Participants were approached for inclusion if they were obtaining an abortion by medication or procedure at less than 12 weeks' gestation. The most common reason for declining was not wanting to return for the postabortion blood draw. Thirty patients with a postabortion sample after 72 hours were included.

Statistical Analysis

The proposed sample size of 500 postabortion samples was based on a 1-sided exact binomial test. The null hypothesis was that 1.5% or more of the postabortion population had fRBC counts exceeding the threshold. Values exceeding 1.5% reflect the historical safety concerns and recommendation for continued use of routine Rh testing. With 500 samples, the null hypothesis would be rejected if fewer than 4 samples (<0.8%) exceeded the threshold, yielding an exact 1-sided type I error rate of .059. The statistical power of this test was 85.7%, assuming that the distribution of individuals exceeding the threshold followed a Poisson distribution with a mean of 0.4% (eMethods in Supplement 1). These hypothesis tests were accompanied by estimates of the rate of participants with fRBC counts exceeding the threshold and a 1-sided 95% CI.[1]

The study design was altered based on the flow cytometry assay optimization and subsequent inclusion of participants undergoing procedural abortions. Thus, we modified our analytic plan to consider whether there were differences in fRBC counts across 3 strata: medication abortion with the original assay, medication abortion with the optimized assay, and procedural abortion with the optimized assay. All participants undergoing procedural abortion were recruited after optimization of the flow cytometry assay. Baseline characteristics of the samples were described overall and by the 3 strata. We tested for differences in the distribution of fRBC counts after abortion between strata using an initial Kruskal-Wallis test, followed by pairwise Wilcoxon rank-sum tests if the global test was significant ($P < .05$). We also used this strategy, with separate analyses for the original or the optimized assay, to consider whether there were differences in fRBC counts before or after abortion between sites or for participants with or without prior bleeding episodes. The time series of fRBC counts was described graphically and summarized by visit using sample means and standard deviations.

To assess the association of postabortion fRBC count with baseline covariates, we fit univariate negative binomial models with postabortion count as the outcome. Each model included the 3 strata (assay by abortion type) as covariates. We explored whether baseline covariates, specifically preabortion fRBC count, maternal age, gestational age, blood type, gravidity, parity, sickle cell heterozygosity, or prior bleeding episodes, were associated with postabortion fRBC counts in this stratified model. All of the covariates, except for blood type, sickle cell heterozygosity, and prior bleeding, were modeled as linear terms. We used Wald tests to evaluate hypotheses regarding the associations. Coefficients in a negative binomial reflect differences on a log scale; to obtain rate ratios, the coefficients and their confidence intervals were exponentiated. These analyses used a 2-sided type I error rate of .05 and confidence intervals were 2-sided with a 95% level. Results are reported using STROBE guidelines.[12] Statistical analyses were conducted using R Version 4.2.1 with the *exactci, MASS, lme4*, and *lmerTest* packages (The R Foundation).

Results

From July 2019 to July 2022, 644 individuals consented to research participation. Evaluable preabortion and postabortion

Table 1. Demographics and Clinical Characteristics of Participants[a]

	No. (%)		
	Medication abortion		
	Original assay (n = 113)	Optimized assay (n = 206)	Procedural abortion (n = 187)
Maternal age, median (range), y	27 (19-39)	27 (18-46)	27 (18-46)
Race[b]			
Black	81 (72)	122 (59)	110/186 (59)
White	15 (13)	56 (27)	52/186 (28)
Other	17 (15)	28 (14)	24/186 (13)
Hispanic or Latino ethnicity	12/92 (13)	38/183 (21)	29/153 (19)
Gestational age, median (range), d	52 (30-70) (n = 111)	47.5 (32-76)	52 (36-78)
Gravidity, median (range)	3 (1-13)	3 (1-19)	4 (1-13)
Parity, median (range)	1 (0-5) (n = 92)	1 (0-8) (n = 159)	1 (0-6) (n = 153)
Blood type			
O	68 (60)	111/205 (54)	91/184 (49)
A	28 (25)	56/205 (27)	56/184 (30)
B	14 (12)	30/205 (15)	32/184 (17)
AB	3 (3)	8/205 (4)	5/184 (3)
Rh negative	13 (11)	16/205 (8)	17/186 (9)
Prior bleeding in pregnancy[c]	27 (24)	34 (17)	34/186 (18)
Sickle cell trait	7/101 (7)	12/194 (6)	6/177 (3)
Site			
Philadelphia Women's Center	94 (83)	48 (23)	90 (48)
Penn Early Pregnancy Access Center	19 (17)	21 (10)	32 (17)
Planned Parenthood League of Massachusetts	0	61 (30)	65 (35)
Delaware County Women's Center	0	76 (37)	0

[a] For full cohort and medication abortion participants separated by preoptimization and postoptimization, see eTable 2 in Supplement 2.

[b] Race was collected by single-answer choice self-report. American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, and other were collapsed into the category "other" due to small numbers in each.

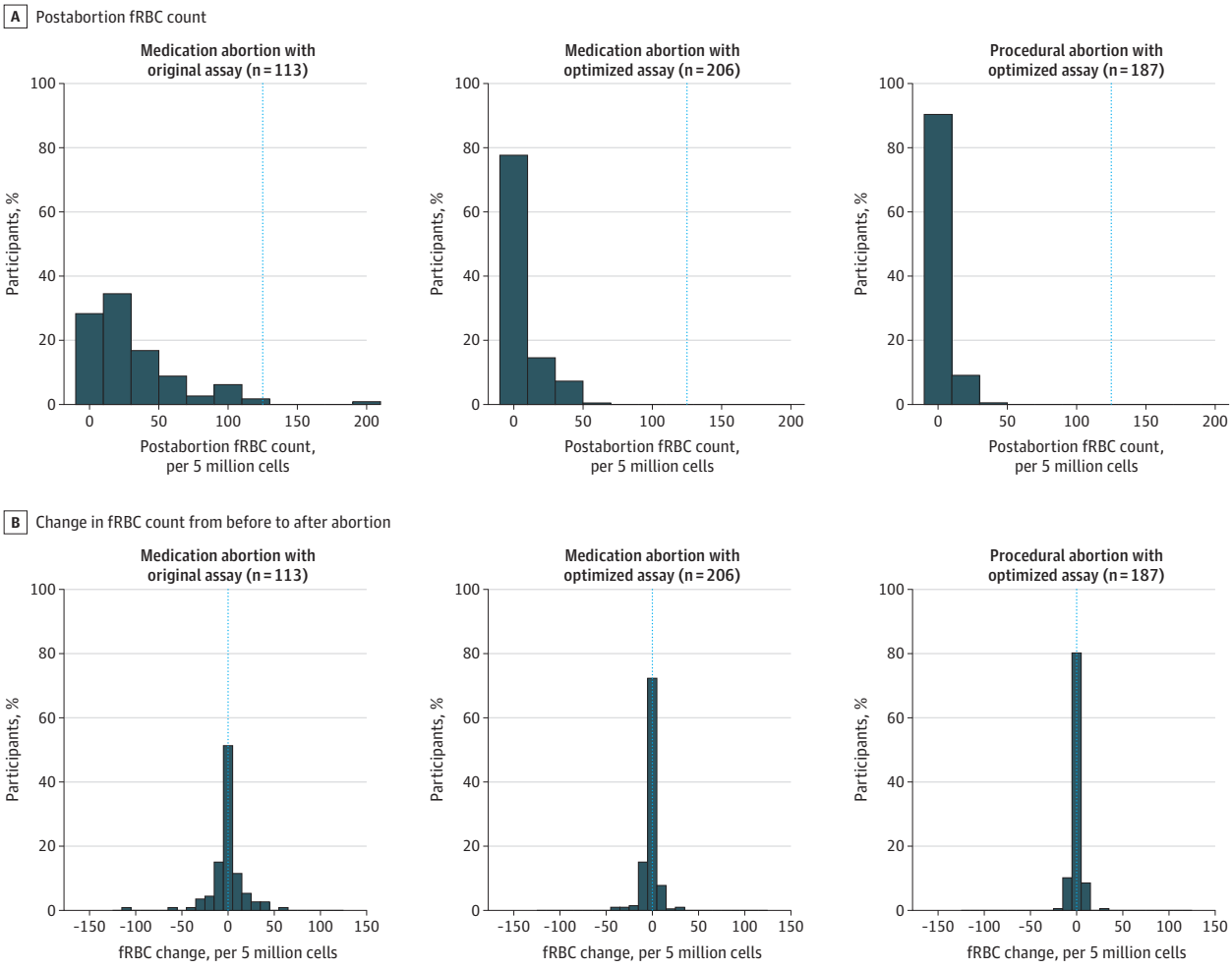
[c] Prior bleeding in pregnancy was by self-report.

phlebotomy samples were obtained from 506 participants (78.9%) (**Table 1**). Across all 506 samples, no participant (0% [95% CI, 0%-0.59%]) had newly elevated fRBC counts above the threshold (P = .004 for the 1-sided exact binomial test). Only 1 participant (0.2% [95% CI, 0%-0.93%]) exceeded the threshold of 125 fRBCs after abortion. That participant had a medication abortion, AB+ blood type, and reported prior bleeding in this pregnancy. She was 1 of 3 participants who were tested using the original (preoptimized) assay who exceeded the fRBC threshold before the intervention (0.6% [95% CI, 0%-1.5%]). The other 2 participants had blood types O− and A+, neither had prior bleeding in this pregnancy, and both fell below the fRBC threshold after the medication abortion. The median fRBC count after abortion was 4.5/5 million cells (**Figure 2**).

Of 319 medication abortion participant samples, 113 (35.4%) were analyzed using the original flow cytometry assay and 206 using the optimized assay (Figure 1). An additional 187 participants undergoing procedural abortion were analyzed using the optimized assay, beginning in September 2021. Using the original assay, the median number of cells after abortion was 21.0/5 million cells (maximum, 191), with 1 of 113 above the threshold for a rate of 0.9% (95% CI, 0%-4.1%). For the optimized assay, the median number of cells was 4.0 (maximum, 58) for the medication group and 3.0 (maximum, 32) for the procedural group; the rates above the fRBC threshold were 0% (95% CI, 0%-1.4%) for medication abortion and 0% (95% CI, 0%-1.6%) for procedural abortion. The distribution of fRBC counts differed significantly among the 3 strata (P < .001, Kruskal-Wallis test), with each of the optimized assay groups differing from the original assay medication abortion group (P < .001 for each, Wilcoxon rank-sum test). We found no statistically significant differences in distribution between medication and procedural postabortion fRBC counts with the optimized assay (P = .10 Wilcoxon rank-sum test). We additionally found no differences in preabortion and postabortion levels between sites for the original (preabortion P = .19, postabortion P = .61; Kruskal-Wallis test) or optimized (preabortion P = .82, postabortion P = .82; Kruskal-Wallis test) assays (eTable 3 in Supplement 1). Among the 6 individuals who underwent the time series analysis, the mean fRBC count before abortion was 5.5 fRBCs/5 million cells (95% CI, 1.9-9.0). We observed only small changes in fRBC counts over time and no systematic pattern of change (eFigure 3 in Supplement 1).

The median change from preabortion to postabortion fRBC counts was 0/5 million cells both overall and for the optimized assay, and 0.5/5 million cells for the original assay. The maximal increase was 28.5 fRBCs/5 million cells for a participant using the original assay. We found no statistically significant differences across strata in the distribution of the change from before vs after abortion (P = .50 Kruskal-Wallis test).

Figure 2. Postabortion Levels of Fetal Red Blood Cell (fRBC) and Change From Preabortion Levels Stratified by Assay and Abortion Type



The bars in the histogram show the percentage for each optimization and abortion method group. The vertical blue line shows the sensitization threshold of 125 fRBCs/5 million cells. Only 1 participant had a postabortion level that exceeded 125 fRBCs/5 million cells.

Table 2 shows the association between baseline covariates and postabortion fRBC counts in univariate models adjusted for type of abortion and assay. Among all baseline covariates considered, only preabortion fRBC counts were strongly associated with postabortion fRBC counts ($P < .001$). An increase of 1 fRBC/5 million cells before abortion was associated with a mean increase of 1.04-fold after abortion (95% CI, 1.03-1.05) (eFigure 4 in Supplement 1). In our cohort, 19% of participants reported bleeding prior to presenting for abortion care, including 1 of the 3 having above-the-threshold fRBC count at baseline. Overall, patients with prior bleeding did not have significantly higher levels of circulating fRBCs after abortion than those without prior bleeding. A Wilcoxon rank-sum test did not indicate differences in the distribution of fRBCs before abortion between those with and without prior bleeding ($P = .90$). Notably, there was no significant increase in fRBC count (per 5 million cells) with gestational age ($P = .14$). **Figure 3** shows the association between postabortion fRBC counts and gestational age. We note that on average, levels in the AB blood group were 1.71-fold (95% CI, 1.05-3.00) higher than in the O blood group ($P = .04$).

Discussion

In this prospective cohort study of 506 individuals receiving first-trimester abortion care, no participant with fRBC counts below the threshold prior to medication or procedural abortion crossed above the threshold after treatment. This study demonstrates that Rh sensitization in the first trimester is very unlikely. When paired with population-based data, these findings are highly reassuring[2,3,5,13] that Rh testing and provision of Rh immune globulin should not be undertaken prior to receiving induced abortion care at less than 12 weeks' gestation.

Rh-negative pregnant individuals may become sensitized and immunized through exposure to Rh-positive RBCs, with risk of sensitization depending on the volume of exposure, number of exposures, ABO compatibility, antigenic

Table 2. Common Association of Postabortion fRBC Counts With Baseline Covariates for a Model With the Strata Defined by Abortion Type and Flow Cytometry Assay

	Rate ratio[a]	*P* value[b]
Preabortion fRBC (per 5 million cells)	1.04 (1.03-1.05)	<.001
Maternal age, y	1.02 (0.87-1.20)	.81
Gestational age, wk	1.05 (0.98-1.12)	.14
Gravida (No. of pregnancies)	0.97 (0.94-1.00)	.08
Parity (No. of births)	1.0 (0.93-1.09)	.88
Sickle cell trait		
None	1 [Reference]	
Unknown (n = 33)	0.81 (0.56-1.21)	.29
Present (n = 25)	0.70 (0.49-1.17)	.18
Blood group		
O (n = 270)	1 [Reference]	
A (n = 140)	1.06 (0.86-1.32)	.58
B (n = 76)	1.12 (0.85-1.48)	.43
AB (n = 16)	1.71 (1.05-3.00)	.04
Prior bleeding		
No (n = 140)	1 [Reference]	
Yes (n = 95)	1.06 (0.84-1.36)	.62
Bleeding postintervention[c]		
Spotting/none	1 [Reference]	
Little	1.29 (0.74-2.23)	.36
Some	1.22 (0.73-1.99)	.43
Moderate	1.17 (0.72-1.83)	.49
Heavy	1.26 (0.77-2.00)	.33

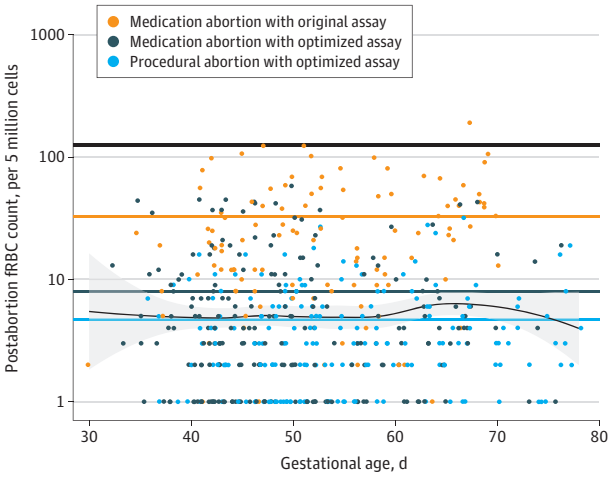
Abbreviation: fRBC, fetal red blood cell.

[a] Rate ratios (95% CI) per 1-unit increase in baseline variable or relative to the reference group. Results based on exponentiated coefficients for a negative binomial model. Values are adjusted for 3 strata (medication abortion with original assay, medication abortion with optimized assay, and procedural abortion with optimized assay).

[b] *P* values based on a Wald test.

[c] Bleeding after medication self-reported by patients from checklist of these choices.

Figure 3. Fetal Red Blood Cell (fRBC) Count After Abortion by Gestational Age



Preoptimization of flow cytometry assay is associated with higher detected levels of postabortion fRBCs (*P* < .001), but gestational age is not (*P* = .14). See Table 2 for details. To display on a log scale (y-axis), a value of 1 was added to any participant with an fRBC level of 0/5 million cells. The solid black line at 125 fRBCs/5 million cells shows the threshold for sensitization. The orange, gray, and blue lines show median values for each optimization and abortion method group. The locally estimated scatterplot smoothing regression curve for the pooled data is show in black with gray shading representing the 95% CI.

profile, immune status, and other factors.[1,13-15] While one might surmise that elevated fRBC counts before abortion were due to a prior exposure, prior bleeding episodes were not found to be associated with elevated fRBC counts. Fetal RBCs from prior pregnancies would have been cleared from the maternal circulation, given their life span of 120 days.[16] The risk of pregnancy-associated Rh sensitization is not increased by induced first-trimester abortion care in this gestational age range.

In this study, postabortion fRBC counts were not correlated with gestational age, gravidity, parity, prior vaginal bleeding in pregnancy, or other demographic factors. The modest increase in postabortion fRBC counts in those with AB blood type over O (rate ratio, 1.71 [95% CI, 1.05-3.00]) merits further study with larger numbers of individuals with AB blood. There was substantial variation in fRBC counts between individuals, but baseline and postabortion fRBC counts were strongly correlated within individuals. Furthermore, a time series analysis of 6 individuals revealed limited variability within individuals and no evidence of significant fRBC count elevation at any of the time points. These findings support the hypothesis that people have different constitutive set points for fRBCs or maternal F cells independent of pregnancy-related bleeding events. This observation deserves further study in pregnant and nonpregnant populations.

The only randomized clinical trial of patients with spontaneous abortion up to 24 weeks' gestation, while underpowered, showed no sensitization in 29 patients receiving placebo, nor Rh-isoimmunization in the 6 subsequent Rh-positive pregnancies.[17] By using flow cytometry, induced abortion at less than 12 weeks' gestation was shown to not put pregnant individuals at risk of sensitization.

The current hypothesis was tested in a population undergoing abortion because the predictable timing of bleeding after induced abortion affords more rigorous study, and every participant had an intervention, whether medication or procedure. Results should be generalizable to many other bleeding events in early pregnancy, including pregnancy loss, which is treated with modalities similar to abortion. In early pregnancy loss, embryonic circulation is halted and thus even less likely to result in fetomaternal hemorrhage than the population studied herein. This study provides additional clinical evidence in support of the longstanding international guidelines that forego Rh immunoglobulin in the setting of spontaneous or threatened miscarriage in the first trimester.[3,7] Additionally, prior bleeding was not associated with higher fRBC counts in this study, further suggesting that patients with threatened or spontaneous abortion are similarly unlikely to be at risk of alloimmunization.

The highest levels of fRBCs, including all 3 patients with fRBC counts above 125/5 million RBCs, were observed in the first-generation flow cytometry assay. Assay optimization allowed for more clear delineation of cell types, suggesting that even those 3 participants may have had falsely elevated fRBC counts, and that the current results are conservative. This is further supported by the results of the 11-color flow cytometry panel, which detected fRBC counts in cryopreserved maternal samples at lower rates than initially detected by the optimized 2-color assay performed on the same samples. The use of more antigens in the 11-color assay allows for more rigorous fRBC classification and removal of non-fRBCs for rare event detection.

The strengths of this study included the large sample size with corresponding statistical power and the use of flow cytometry with large event counts (5 million) to quantify the level of maternal exposure to fRBCs. A broad demographic range of patients was included, with real-world exposures including prior uterine bleeding during pregnancy, all blood types, and numerous clinical situations. Additionally, the current methods were tested to validate the chosen timeframe for post-abortion blood draw to ensure that the peak value of circulating fRBCs was not missing, finding no evident increase in fRBC counts at finer time intervals up to 72 hours after abortion.

This study provides evidence to inform guidelines that deimplement Rh testing following induced abortion in the first trimester. National and international guidelines can follow the World Health Organization recommendation to forego Rh testing and treatment at less than 12 weeks' gestation, in support of high-value care.[5,18] Given the evolving induced abortion policy landscape in the United States, provision of induced abortion care must be as efficient, cost-effective, and evidence-based as possible.

Limitations

This study had several limitations. First and most significantly, the true threshold for Rh sensitization is unknown and likely multifactorial. Even use of the most conservative threshold is a proxy for the clinical outcome that truly matters: hemolytic disease of the newborn resulting from alloimmunization in a prior pregnancy. However, a prospective study to measure this risk lacks feasibility. A best estimate was used based on prior studies and the volume dependency of Rh immunoglobulin for efficacy.[10,19,20] The within-person pre/post design mitigates the concern that the chosen threshold was incorrect because not only were nearly all fRBC counts far below the threshold, but they did not change before vs after abortion, irrespective of the threshold.

Second, the development of the flow cytometry protocol was an iterative process that may continue to evolve with time and further understanding of RBC antigens and immunobiology.

Third, patients experiencing other causes of bleeding in the first trimester, such as ectopic pregnancy or molar pregnancy, were not included, thus limiting generalizability to these clinical scenarios.

Fourth, the SARS-CoV-2 pandemic took place midway through the study, hampering recruitment. However, this challenge was overcome by expanding the study question to include participants undergoing procedural abortion, thereby improving recruitment and increasing generalizability.

Conclusions

Induced abortion in the first trimester, whether by medication or procedure, is not a risk factor for Rh sensitization. This financial and clinical barrier to abortion care is not necessary. This evidence should inform the alignment of international guidelines and clinical care surrounding Rh immunoglobulin following first-trimester induced abortion.

ARTICLE INFORMATION

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Author Contributions: Drs Luning Prak and Schreiber had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Luning Prak and Schreiber contributed equally.
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Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Horvath, Huang, Koelper, Putt, Luning Prak, Schreiber.
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Supervision: Horvath, Huang, Tsao, Zhao, Goldberg, Hannum, Luning Prak, Schreiber.

Conflict of Interest Disclosures: Dr Goldberg reported serving as chair of the Society of Family Planning Complex Family Planning Advisory Council (2019-2020) outside the submitted work. Dr Schreiber reported receiving contracts from Athenium Pharmaceuticals and the National Institutes of Health and grants from Independence Blue Cross outside the submitted work; in addition, Dr Schreiber had a patent (19-8815) issued for medical management of nonviable pregnancy and a patent (18-8692) with royalties paid. No other disclosures were reported.

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