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Prospective quantification of fetomaternal hemorrhage with dilation and evacuation procedures

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ABSTRACT

Objective: To describe fetomaternal hemorrhage (FMH) during second-trimester dilation and evacuation (D&E) to evaluate if Rhesus-immune globulin (RhIG) 100 mcg (used in the United Kingdom) and 300 mcg (used in the United States) provide adequate prophylaxis.
Study design: We conducted an exploratory prospective descriptive study of women undergoing D&E between 15 weeks 0 days and 23 weeks 6 days of gestation. Enrolled participants had Kleihauer–Betke testing on specimens obtained before and after D&E. We assessed the main outcome measures of FMH in mL suggesting need for more than 100 mcg and 300 mcg RhIG (FMH of 10 mL and 30 mL fetal whole blood, respectively) and association of postprocedure FMH with demographic characteristics and procedure-related variables.
Results: The 300 participants had a mean gestational age of 19 weeks 6 days±2 weeks 2 days. The median preprocedure FMH was 0 mL (range 0–50 mL) with 2 (0.67%) women exceeding 10 mL (19 mL and 50 mL). The median postprocedure FMH was 1 mL (range 0–60 mL). Almost all participants had postprocedure FMH <10 mL (n=295, 98.3%) and <30 mL (n=298, 99.3%). All participants under 18 weeks had FMH <10 mL. We found no demographic or procedure-related factors to be predictive of FMH quantity.
Conclusions: FMH occurring with routine second-trimester D&E procedures is minimal. Adequate prophylaxis with RhIG 100 mcg and 300 mcg occurred in >98% of women and in all cases <18 weeks of gestation. This study is the first step to potentially reducing the dose and costs of RhIG administration with D&E.
Implications: This study is a first step in quantifying fetomaternal hemorrhage with routine dilation and evacuation procedures; larger trials are needed, especially to understand why some women have recognizable hemorrhage preprocedure. If dosing requirements are too high with current guidelines, lower doses will result in resource and cost savings.

1. Introduction

Fetomaternal hemorrhage (FMH) occurs when fetal cells enter the maternal circulation during events such as amniocentesis, trauma, abortion procedures and delivery and can lead to immune sensitization in Rhesus (Rh)-negative women. Standard care includes Rh-immune globulin (IG) administration to unsensitized Rh-negative women to prevent maternal isoimmunization during any potentially sensitizing event or when FMH is suspected.

RhIG is crucial in prevention of isoimmunization and possible fetal morbidity in subsequent pregnancies, with timely administration preventing 80%–90% of isoimmunization [1,2]. Since the 1970s, countries with Rh-prophylaxis guidelines have seen significant decreases in isoimmunization and hemolytic disease of the fetus and newborn. However, guidelines from various national societies differ in recommended dosing and timing of administration during pregnancy and other potentially sensitizing events [3]. Notably, UK second-trimester guidelines recommend RhIG 50 mcg for any potentially sensitizing event until 20 weeks of gestation and RhIG 100 mcg thereafter in conjunction with FMH quantification [4]. Conversely, US guidelines recommend a 300-mcg dose with any potentially sensitizing event at 12 or more weeks of gestation [1]. These variable RhIG doses correlate with FMH of fetal whole blood into the maternal circulation of 5 mL, 10 mL and 30 mL for RhIG 50 mcg, 100 mcg and 300 mcg, respectively. Despite the discrepancy, initial studies dating back to the 1970s indicate that both the UK and US dosing

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regimens similarly decrease isoimmunization and hemolytic disease of the fetus and newborn [1,5].

The only available second-trimester FMH data primarily include induction abortions for fetal anomalies [6,7], and no studies specifically evaluate FMH with dilation and evacuation (D&E). Given recent RhIG shortages around the world such as in Australia and Poland [8,9], and the cost of higher doses of RhIG to healthcare systems, we sought to begin to understand if a RhIG dose less than 300 mcg might be sufficient in the second trimester. We designed this study to evaluate FMH with routine D&E from 15 weeks 0 days to 23 weeks 6 days of gestation using Kleihauer–Betke (KB) acid elution testing.

2. Materials and methods

From February 2016 to April 2017, we approached patients in our outpatient clinic for possible study participation during a preoperative evaluation with planned cervical osmotic dilator placement to be followed the next day by D&E. We included women with a singleton pregnancy who would be 15 weeks 0 days to 23 weeks 6 days of gestation on the day of their procedure based on the clinical preoperative evaluation using standard obstetrical dating and abdominal ultrasound examination. We excluded women with a fetal demise, incarcerated women and women unable to consent for themselves. The University of California, Davis, Institutional Review Board approved the study, and all subjects signed written informed consent after signing consent for the abortion and prior to cervical preparation.

We used Dilapan-S® (MEDICEM Technology, s.r.o., Czech Republic) synthetic osmotic dilators for cervical preparation based on a standardized gestational-age-based protocol for all providers (Online Appendix 1). Providers could also use adjunctive mifepristone 200 mg orally or misoprostol 400 mcg vaginally per their clinical judgment.

We obtained preprocedure blood samples at the time of intravenous line placement in the preoperative area prior to the D&E. We defined the procedure start as the time the first instrument passed into the uterus (rigid dilators, suction cannula or forceps) and end as the time the last instrument related to the D&E procedure was removed from the uterus. If postprocedure intrauterine device placement occurred, that time was not included in total procedure time. One of five fellowship-trained Family Planning attending physicians performed or supervised fellows, residents or medical students for each case.

We obtained a postprocedure blood sample between 30 and 120 min after the procedure ended. Rh-negative participants received RhIG 300 mcg after obtaining the postprocedure blood sample. We withdrew enrolled participants for whom a postprocedure blood sample could not be obtained after three attempts or those who required additional postoperative procedures for hemorrhage, including intrauterine balloon placement or blood transfusion.

We measured FMH using KB acid elution testing. To limit interreader variability, one of three hematology senior clinical laboratory scientists devoted to the study performed and read the KB tests in batches. The lead laboratory scientist reread any KB tests with an abnormal result.

The primary objective of this study is to describe the amount of FMH occurring with routine D&E from 15 weeks 0 days to 23 weeks 6 days of gestation. We aimed to describe preprocedure FMH amounts, the proportion of participants with FMH less than 10 mL and 30 mL of fetal whole blood in maternal circulation, and potential associations between amount of FMH and estimated blood loss, gestational age, procedure time, fetal anomalies, blood type and Rh status. We also assessed the proportion of women through 20 weeks 0 days of gestation with FMH less than 5 mL.

We estimated a convenience sample size based on the assumption that 100% of samples would demonstrate an FMH of less than 10 mL, the amount covered by RhIG 100 mcg. A sample of 300 women provided the lower bounds of a 95% confidence interval of no less than 99%. Enrollment occurred until 300 pre- and postprocedure specimens were completed and analyzed. We performed χ^2 and Fisher's Exact Tests for categorical outcomes and Spearman correlations for continuous and categorical outcomes as appropriate using SAS software version 9.4® (SAS Institute Inc., Cary, NC, USA). We considered a p value less than .05 as significant.

3. Results

We identified 386 potential participants during the study period who met study inclusion criteria, of whom 61 declined study participation. Of the 325 enrolled women, 15 discontinued prior to D&E (withdrew consent or did not complete abortion procedure), 2 had postprocedure samples which could not be evaluated, and 6 did not have postprocedure samples. We excluded 2 women who had additional postprocedure interventions for bleeding, leaving 300 women in the analysis.

Baseline characteristics of the study population are presented in Table 1. Notably, about half (51.3%) of the study participants had pregnancies at 20 weeks and above (median gestational age 20 weeks 0 days). Preoperative and intraoperative characteristics which could potentially affect FMH are presented in Table 2.

Postprocedure phlebotomy for FMH testing occurred at a median of 37 min (range 30–112 min) after the procedure. Median postprocedure FMH was 1 mL (range 0–60 mL). Five (1.67%, 95% CI 0.22%–3.12%) participants had postprocedure FMH greater than 10 mL (Table 3), two (0.67%, 95% CI 0%–1.59%) of whom also had postprocedure FMH equal to or greater than 30 mL. Of those five participants, two had a gestational age between 18 and 20 weeks, and three greater than 20 weeks. None of the 64 women at less than 18 weeks of gestation and none of the 8 women who received adjunctive mifepristone or misoprostol had an FMH that exceeded 10 mL.

Table 1
Demographic, obstetric and hematologic characteristics of women having abortion who had pre- and postprocedure Kleihauer–Betke testing (N=300)

Characteristic	n (%) or mean ± SD	Range
Age (years)	27.1±6.7	14–44
BMI (kg/m^2)	28.7±6.9	14.7–58.7
Gestational age (days)	139.1±16.1	105–167
Non-Hispanic ethnicity	212 (70.1)	
Race		
White	163 (54.3)	
Black	70 (23.3)	
Asian	18 (6.0)	
Other	49 (16.3)	
Gravidity		1–15
1	66 (22.0)	
2	39 (13.0)	
3	52 (17.3)	
4	44 (14.7)	
5–6	55 (18.3)	
7 or more	44 (14.7)	
Prior vaginal delivery		0–7
0	131 (43.7)	
1	61 (20.3)	
2	64 (21.3)	
3 or more	44 (14.7)	
Prior cesarean delivery		0–4
0	229 (76.3)	
1	41 (13.7)	
2	17 (5.7)	
3 or more	13 (4.3)	
Prior spontaneous abortion	76 (25.3)	0–4
Prior induced abortion	146 (48.7)	0–6
Suspected morbidly adherent placenta	16 (5.3)	
Fetal anomaly indication for abortion	39 (13.0)	
Blood type		
A	102 (34.0)	
AB	5 (1.7)	
B	41 (13.7)	
O	152 (50.7)	
Rhesus-negative	27 (9.0)	

Table 2
Preoperative and intraoperative characteristics of dilation and evacuation procedures (N=300)

Characteristic	n (%) or median (range)
Preoperative	
Cervical dilator per standard protocol	300 (100%)
Adjunctive mifepristone	4 (1.3%)
Adjunctive misoprostol	4 (1.3%)
Heavy bleeding between cervical preparation and preprocedure phlebotomy	0
Intraoperative	
Heavy bleeding after dilator removal	0
Procedure time (min)	15 (5–51)
Estimated blood loss (mL)	100 (5–2000)
Uterotonic use	42 (14.0)
Complications	20 (6.7%)
Cervical laceration	15
Hemorrhage	5

Of the 146 women at 20 weeks 0 days of gestation or less, 10 (6.85%, 95% CI 2.75%–10.95%) had postprocedure FMH over 5 mL. None of the 24 women at less than 16 weeks of gestation had an FMH that exceeded 5 mL.

Preprocedure phlebotomy for FMH testing occurred with all specimens obtained within 120 min prior to procedure. Thirty-two (12%, 95% CI 7.17%–14.16%) women had detectable FMH preprocedure with a median baseline FMH of 0.00 mL (range 0–50 mL). FMH exceeded 5 mL, 10 mL and 30 mL in four (1.33%, 95% CI 0.04%–2.63%), two (0.67%, 95% CI 0%–1.59%) and one (0.33%, 95% CI 0%–0.99%) participant(s), respectively (Table 3). The two cases exceeding 10 mL also had postprocedure FMH >10 mL; neither of these cases had significant vaginal or uterine bleeding noted at cervical dilator placement or removal.

We found no significant associations between demographic characteristics or procedure-related variables and postprocedure FMH (Table 4).

4. Discussion

We found that the amount of FMH occurring with routine second-trimester D&E procedures as measured using KB testing is minimal and adequately covered by RhIG 100 mcg in most cases. Only 12% of participants had any detectable FMH prior to the procedure. No patients under 18 weeks in our study would have needed a RhIG dose exceeding 100 mcg. Unexpectedly, 7% of women under 20 weeks of gestation had postprocedure FMH exceeding 5 mL, which raises concern that the UK dosing guidelines of RhIG 50 mcg through 20 weeks gestation may not be adequate in some cases. We found no significant relationships between postprocedure FMH and gestational age, estimated blood loss, prior pregnancy history, blood type, Rh status or presence of a fetal anomaly.

Our study provides a unique contribution to our knowledge of FMH during second-trimester abortion. The only prior study specifically evaluating FMH with second-trimester abortions included 67 women with fetal anomalies; all but 5 women underwent labor induction abortion [6]. A 1969 study compared “fetal cell scores” in women having sharp curettage procedures for pregnancy loss or abortion to controls who did not have a procedure [7]. The authors presented data based on type of pregnancy loss (threatened versus incomplete), by treatment method for abortion patients and by gestational age for the control group (<16 weeks and 16–40 weeks). However, the authors did not stratify data by gestational age for the pregnancy loss or abortion groups.

A strength of our study is that we employed a wide range of providers and learners during the procedures with varying skill levels, so our findings are generalizable. We also minimized interreader variation when reading KB slides by employing only three readers during the study. We chose not to evaluate preprocedure FMH prior to cervical preparation; as such, we may have missed any relationship of the elevated preprocedure FMH evaluations to dilator placement. Theoretically, dilator placement has the potential to cause FMH. None of our participants reported any heavy bleeding after dilator placement, and no physicians reported heavy bleeding after cervical dilator removal.

Table 3
Women with FMH exceeding 5 mL by Kleihauer–Betke testing before or after a dilation and evacuation procedure[a]

Gestational age	Preprocedure FMH (mL)	Postprocedure FMH (mL)
19w4d	0.0	5.5
16w4d	0.0	6.5
19w5d	0.0	8.5
19w2d	2.5	5.5
19w5d	5.5	6.0
17w5d	3.0	7.0
19w5d	6.5	7.0
19w3d	2.0	8.5
22w0d	0.0	10.5
18w2d	5.0	12.5
21w1d	19.0	24.0
23w0d	0.0	30.0
19w2d	50.0	60.0

w, weeks; d, days.
[a] 5 mL for women 15w0d through 20w0d; 10 mL and 30 mL for women 15w0d through 23 w6d.

Table 4
Statistical significance between demographic and procedure-related variables and postprocedure FMH >10 mL in women having a D&E procedure

Variable	Number	FMH >10 mL	p value
Gestational age			.59
<18 weeks	64	0	
≥18 weeks	236	5 (1.7%)	
BMI			.51
<30 kg/m^2	193	4 (1.3%)	
≥30 kg/m^2	107	1 (0.3%)	
Gravidity			.15
1–3	157	3 (1.0%)	
4–15	143	2 (0.7%)	
Prior vaginal delivery	169	2 (0.7%)	.24
Prior cesarean delivery	71	0	.16
Prior miscarriage	76	1 (0.3%)	.18
Prior abortion	146	2 (0.7%)	.08
Ethnicity			.57
Hispanic	77	1 (0.3%)	
Non-Hispanic	212	4 (1.3%)	
None reported	11	0	
Race			.25
White	163	4 (1.3%)	
Nonwhite	137	1 (0.3%)	
Blood type			.24
A	102	1 (0.3%)	
B	41	1 (0.3%)	
AB	5	0	
O	152	3 (1.0%)	
Rh-status			.59
Positive	273	5 (1.7%)	
Negative	27	0	
Fetal anomaly indication for abortion	39	1 (0.3%)	.87
Adjunct cervical preparation			
Mifepristone	4	0	.43
Misoprostol	4	0	.13
Estimated blood loss			.77
<100 mL	125	2 (0.7%)	
≥100 mL	175	3 (1.0%)	
Procedure time			.87
<15 min	137	2 (0.7%)	
≥15 min	163	3 (1.0%)	
Uterotonic use	42	0	.37

All data presented as n (%).

We did not screen for baseline hemoglobinopathies (e.g., β-thalassemia and sickle cell disease) that may falsely elevate KB results due to persistent or high Hgb F levels. Interestingly, two of the five women with FMH greater than 10 mL also had detectable baseline FMH exceeding 10 mL, which could reflect an underlying medical condition that affects KB results rather than a result of the procedure itself. Future studies should screen for hemoglobinopathies or reflex test for hemoglobinopathies if an excessive amount of HgbF cells is found on KB.

Flow cytometry may be a more accurate method of determining FMH with decreased interuser variation and greater precision once appropriate protocols are set in place. We elected to use KB testing rather than flow cytometry because KB testing is more generalizable as the most widespread and accessible quantification method in clinical laboratories worldwide [10].

This exploratory study provides a large sample for the quantification of FMH with second-trimester D&E. FMH in routine second-trimester D&E procedures is small and adequately prophylaxed by RhIG 100 mcg as is used in the UK. The US guideline recommended RhIG 300-mcg dose is excessive in virtually all cases. Although this study begins to address the important question of how much RhIG is actually needed for these procedures, it is not large enough to definitively change current practice. Future studies are needed before changing dosing recommendations and might include a direct comparison of FMH using KB and flow cytometry, or evaluation of how much FMH occurs with dilator placement. Although our findings also suggest that the UK dosing recommendations of 50 mcg through 20 weeks may need further assessment, no available data support that women who receive this dose at 16–20 weeks of gestation have higher isoimmunization rates. In time, reducing the excess amount of RhIG used unnecessarily can help preserve a finite resource and lower healthcare costs.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.contraception.2018.11.015.

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References

[1] American College of Obstetricians and Gynecologists. ACOG practice bulletin no. 181: prevention of Rh D alloimmunization. Clinical management guidelines for obstetrician-gynecologists. Obstet Gynecol 2017;130(2):e57–70.
[2] Freda VJ, Gorman JG, Pollack W, Bowe E. Prevention of Rh hemolytic disease — ten years' clinical experience with Rh immune globulin. N Engl J Med 1975;292(19):1014–6.
[3] Sperling JD, Dahlke JD, Sutton D, Gonzalez JM, Chauhan SP. Prevention of RhD alloimmunization: a comparison of four national guidelines. Am J Perinatol 2018;35(2):110–9.
[4] Qureshi H, Massey E, Kirwan D, Davies T, Robson S, White J, et al. BCSH guideline for the use of anti-D immunoglobulin for the prevention of haemolytic disease of the fetus and newborn. Transfus Med 2014;24(1):8–20.
[5] McMaster conference on prevention of Rh immunization 28–30 September, 1977, Vox Sang 1979;36(1):50–64.
[6] Merz W, Patzwaldt F, Fimmers R, Stoffel-Wagner B, Gembruch U. Fetomaternal hemorrhage in the second trimester. J Perinat Med 2012;40(4):353–6.
[7] Katz J. Transplacental passage of fetal red cells in abortion; increased incidence after curettage and effect of oxytocic drugs. Br Med J 1969;4(5675):84–6.
[8] Dean M. Wanted: Rh D negative donors. Aust Provid 2000;23(2):36–8.
[9] Cuker A. Are 25 antibodies better than 1? Blood 2012;120(18):3627–8.
[10] Sandler SG, Sathiyamoorthy S. Laboratory methods for Rh immunoprophylaxis: a review. Immunohematology 2010;26(3):92–103.