Effects of Prophylactic Oxytocin on Bleeding Outcomes in Women Undergoing Dilation and Evacuation

A Randomized Controlled Trial

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OBJECTIVE: To estimate whether routine use of intravenous oxytocin decreases the frequency of interventions to control excess blood loss during dilation and evacuation (D&E).

METHODS: In this multisite, randomized, double-blind, placebo-controlled trial, women undergoing D&E at 18–24 weeks of gestation received 30 units of oxytocin in 500 mL of intravenous fluid or 500 mL of intravenous fluid alone initiated on speculum placement. The primary outcome was the frequency of interventions to control excess bleeding. A sample size of 75 patients per group was needed to detect a 15% decrease in intervention from 20% to 5% with 80% power and two-sided alpha 0.05. Secondary outcomes included measured blood loss, complications, procedure duration, postoperative pain, and patient satisfaction.

RESULTS: From November 2014 to February 2018, we screened 337 women and randomized 160 to receive prophylactic oxytocin (n=82) or placebo (n=78). Demographic characteristics were similar between groups. The frequency of interventions for bleeding, our primary outcome, was 7.3% in the oxytocin group vs 16.7% in the placebo group, difference of 9.4% (95% CI −21.0% to 1.9%). Interventions primarily included uterine massage and uterotonic administration. Among our secondary outcomes, median measured blood loss was lower in the oxytocin group at 152 (interquartile range 98–235) mL vs 317 (interquartile range 168–464) mL (95% CI 71.6–181.5). Frequency of hemorrhage, defined as blood loss of 500 mL or more and 1,000 mL or more, was lower in the oxytocin group at 3.7% vs 21.8%, difference of 18% (95% CI −29 to −6.9%) and 1.2% vs 10.3%, difference of 9.0% (95% CI −17 to −0.7%), respectively. Procedures were shorter in the oxytocin group at a median of 11.0 (interquartile range 8.0–14.0) vs 13.5 (interquartile range 10.0–19.0) minutes in the placebo group (95% CI 1.0–4.0). We found no differences in the frequency of nonhemorrhage complications, pain scores, or satisfaction scores between groups.

CONCLUSION: Prophylactic use of oxytocin during D&E at 18–24 weeks of gestation did not decrease the frequency of interventions to control bleeding. However, oxytocin did decrease blood loss and frequency of hemorrhage.

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Hemorrhage, generally defined as blood loss greater than 500 mL, is the most common complication of dilation and evacuation (D&E), occurring in 0.8–3.2% of all procedures.[1–3] Hemorrhage risk increases with gestational age, affecting up to 6.3% of D&Es performed above 18 weeks of gestation.[4] In an attempt to decrease blood loss and hemorrhage at the time of the procedure, some abortion providers routinely administer uterotonics, including oxytocin.[5] The ability of oxytocin to decrease bleeding is extrapolated from the obstetric literature, but has questionable biological plausibility in the late second and early third trimesters. Uterine oxytocin receptor concentration does not increase significantly until approximately 37 weeks of gestation and receptors are not fully expressed until a woman is in labor.[6,7] Studies evaluating routine oxytocin for first trimester surgical abortion failed to show any significant effect on blood loss.[8,9] To date, no randomized trials have evaluated routine oxytocin administration at the time of D&E.

We were unable to find any published reports of adverse events associated with oxytocin use at the time of D&E. However, when used during labor and delivery or induction abortion, oxytocin-related complications such as anaphylaxis, uterine rupture, arrhythmias, and water intoxication have been reported.[10–13]

Given the lack of evidence supporting routine use of oxytocin to prevent excess bleeding during D&E, we conducted a randomized, double-blind, placebo-controlled trial to evaluate the effect of oxytocin on bleeding outcomes. We aimed to determine whether routine use of intravenous oxytocin decreases the rate at which providers must intervene to control excess blood loss during D&E.

METHODS

We conducted a multisite, randomized, double-blind, placebo-controlled trial at the University of Hawaii, Honolulu, Hawaii, and the University of Washington, Seattle, Washington. Surgeons performed D&E procedures at the University of Hawaii in an ambulatory surgical center and at University of Washington in a freestanding clinic setting. The Queens Medical Center Research & Institutional Review Committee (Honolulu, Hawaii), University of Hawaii Committee on Human Studies, and the University of Washington Human Subjects Division approved our study.

Study staff approached and consented potential patients at the preoperative visit or on the day of surgery after women had received abortion counseling and provided consent for D&E. Women, aged 14–50 years, who were willing and able to sign consents in English or Spanish were eligible if they were having a D&E at 18–24 weeks of gestation. We included patients with intrauterine fetal demise. We determined gestational age via ultrasound measurements according to the standard of care. We excluded those with multiple gestation, history of coagulopathy, anticoagulant use in the preceding five days, known uterine anomalies, chorioamnionitis or sepsis, suspected placenta accreta, or use of misoprostol for cervical preparation. We recorded medical history and demographic characteristics.

A researcher not directly involved in the study prepared a computer-generated random number scheme specific to each site in random varying block sizes of four, six, and eight, and placed them in sequentially numbered sealed, opaque envelopes. Research pharmacists at the respective institutions performed allocation. All but the research pharmacist were blinded to treatment assignment.

According to the standard of care at each site, patients received 1 to 2 days of overnight dilators for cervical preparation and prophylactic antibiotics before their procedure. At the University of Hawaii, four experienced D&E providers and four Family Planning fellows performed study procedures. At the University of Washington, four experienced D&E providers, four Family Planning fellows, and third-year obstetrics and gynecology residents performed procedures. All trainees worked under direct faculty supervision.

Within 60 minutes of starting the procedure, study staff assessed patients' baseline pain score using a 10-cm visual analog scale and overall patient satisfaction with the abortion experience thus far using a five-point Likert scale. We obtained this assessment while cervical dilators were still in place, but before any analgesic medications were given. Study staff delivered identical appearing study medications, (treatment arm: 500 mL of in vitro fertilization with 30 units of oxytocin; control: 500 mL of intravenous fluid) labeled only with study identification numbers to the procedure room. Each patient received general anesthesia (including the use of halogenated gases) or deep sedation, with choice and dosage of anesthetic agents decided by the anesthesia provider (anesthesiologist or certified registered nurse anesthetist).

Providers performed D&Es under direct ultrasound guidance. On speculum insertion, the anesthesia provider began administering the study drug as an intravenous fluid bolus infusion over approximately 15 minutes. All patients were given five units of vasopressin mixed with 10 mL of saline or local anesthetic in a paracervical block injected at the 4- and 8-o'clock positions.[2,14,15] If indicated, serial cervical dilation

Box 1. Algorithm of Interventions to Control Bleeding

1. Bimanual uterine massage
2. Intramuscular methylergonovine 0.2 mg (may repeat dose in 2–4 h)
3. Rectal misoprostol 800 micrograms
4. Two hundred fifity micrograms of intramuscular carboprost tromethamine (may repeat dose every 15–90 min)
5. Intrauterine balloon tamponade
6. Laparoscopy, laparotomy, embolization

*Additional injections of vasopressin may be used at provider's discretion to control bleeding at any time.

Authors' Data Sharing Statement

Will individual participant data be available (including data dictionaries)? *No.*

What data in particular will be shared: *Not available.*

What other documents will be available? *Not available.*

When will data be available (start and end dates)? *Not applicable.*

By what access criteria will data be shared (including with whom, for what types of analyses, and by what mechanism)? *Not applicable.*

was performed. Surgeons drained amniotic fluid until ultrasonography demonstrated that the uterus was empty of fluid and set this fluid aside to begin blood loss measurement.

Our primary outcome was rate of provider interventions (defined in Box 1) to control excess bleeding during D&E. The decision to intervene was based on clinical judgment and signs of impending hemorrhage such as brisk or prolonged vaginal bleeding or signs of hemodynamic instability. Surgeons taking part in the study agreed on and were trained at study initiation to use an evidence-based algorithm (Box 1) when intervening to control excess blood loss; we noted deviations from the algorithm or contraindications to mediations when applicable.[2] We documented any complications, defined as hemorrhage (blood loss of 500 mL or more), cervical laceration, uterine perforation and any resulting intra-abdominal injury, blood transfusion, drug reaction, and death, that occurred both intraoperatively and postoperatively until discharge. Procedure time was recorded in minutes from the time of speculum placement to speculum removal. If a woman received a postabortion intrauterine device, we stopped the timer before placement when the D&E portion of the procedure was complete.

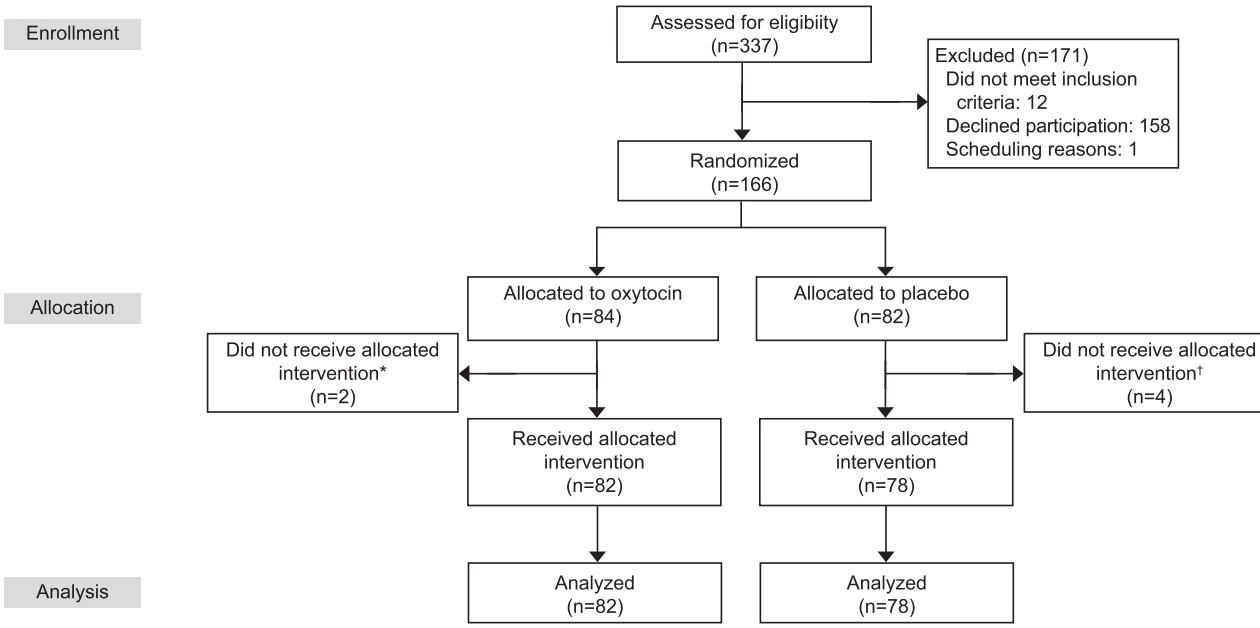

Fig. 1. Flow diagram. *One participant was rescheduled for a different day when the study medication was not available, and the other participant was deemed unable to receive 500 mL of intravenous fluid by the anesthesiologist owing to a cardiac condition. †Two participants needed preoperative misoprostol and thus met exclusion criteria, one participant's procedure was canceled because she had not fasted, and another participant withdrew study consent.

Whitehouse: Prophylactic Oxytocin During D&E. Obstet Gynecol 2019.

We performed a measured blood loss in the following fashion: a strainer was used to separate products of conception and blood so that volume of blood could be measured; gauze and sponges were weighed to determine additional blood loss. Postoperatively, we weighed any used pads and other blood-soiled materials to quantify bleeding up until the time of discharge.

Staff gave women 15 mg of intravenous ketorolac or 500 mg of oral naproxen, unless contraindications existed, and administered additional pain medications or antiemetics as needed to achieve optimal patient comfort. Approximately 60 minutes after procedure completion, study staff assessed overall patient satisfaction with the abortion experience and postoperative pain scores.

Our primary outcome was the rate of interventions to control blood loss. We believed this outcome was more clinically relevant than blood loss because it is unclear what amount of blood loss is clinically meaningful in the D&E population. We felt that measuring the need for additional interventions would allow a comparison of the clinical consequences of use or nonuse of prophylactic oxytocin. Our rationale for study sample size was based on a study by Micks et al,[16] in which investigators used the same primary outcome and found a baseline need for intervention of 16% when skilled abortion providers performed D&E procedures. Because trainees participated in almost all procedures performed at our institutions, we estimated our rate of intervention would be higher at approximately 20%. We hypothesized that, if oxytocin had clinically significant effects, it would cause a decrease in intervention rates from 20% to 5%. We calculated a sample size of 75 patients per group to demonstrate this difference of 15%, with 80% power and two-sided alpha 0.05. To account for a 10% dropout rate, we planned to randomize 83 patients to each group for a total enrollment of 166 patients.

We analyzed data with R 3.0.3 and SAS (Statistical Analysis System) 9.4. We compared differences in proportions and 95% CIs for bleeding interventions between treatment and placebo groups using the Fleiss method. Median measured blood loss, procedure length, pain and satisfaction scores, and their 95% CIs were calculated for both groups using the Hodges Lehmann procedure and assessed for normality. Continuous demographic variables were compared using a Student *t*-test. We compared the proportions of complications and other categorical outcomes and corresponding 95% CIs using the Fleiss method. Categorical demographic variables were compared using a χ^2 test or Fisher exact test as applicable. We followed an intention-to-treat analysis.

Table 1. Characteristics of Women Undergoing Dilation and Evacuation, Comparing Those Who Received Oxytocin With Those Who Received Placebo

Demographic	Oxytocin (n=82)	Placebo (n=78)
Age (y)	25.4±7.0	27.2±7.2
Gestational age (wk)	19 6/7±9.3 d	20 2/7±10.4 d
Gestational age groups (wk)		
18–19 6/7	40 (48.8)	34 (43.6)
20–21 6/7	36 (46.3)	34 (43.6)
22–23 6/7	6 (7.3)	10 (7.8)
24 and up	0	0
Race–ethnicity		
White	32 (39.0)	36 (46.2)
Asian	27 (32.9)	32 (41.0)
Black	10 (12.2)	5 (6.4)
Hispanic or Latina	8 (9.8)	8 (10.3)
Native Hawaiian or Pacific Islander	20 (24.4)	23 (29.5)
American Indian or Alaska Native	6 (7.3)	5 (6.4)
Other	0	2 (2.6)
Nulliparous	38 (46.3)	36 (46.2)
History of cesarean delivery	6 (7.3)	10 (12.8)
BMI (kg/m^2) 30 or greater	12 (14.6)	22 (28.2)
Cigarette smoker	31 (37.8)	33 (42.3)
Intrauterine fetal demise	2 (2.4)	3 (3.9)
Fetal anomaly	7 (8.5)	9 (11.5)
No. of preoperative laminaria	5.4±1.9	5.6±2.0
Type of anesthesia used		
Conscious sedation	26 (31.7)	22 (28.2)
General anesthesia	56 (68.3)	55 (70.5)
Postoperative LARC placement	29 (35.4)	26 (33.3)
Trainee involvement in procedure*	50 (61.0)	54 (69.2)
Site		
University of Hawaii	56 (68.3)	56 (71.8)
University of Washington	26 (31.7)	22 (28.2)

BMI, body mass index; LARC, long-acting reversible contraception.
Data are mean±SD or n (%).
* Includes fellow or resident physician.

RESULTS

From November 2014 to February 2018, a total of 337 women were screened, and 166 patients were enrolled and randomized (84 oxytocin group, 82 placebo group). Flow of participants is shown in Figure 1. Baseline and demographic characteristics were similar between groups (Table 1) aside from a three-day difference in gestational age (P=.05). We found no difference in use of halogenated gases between treatment arms.

Table 2. Blood Loss, Interventions, Complications, and Procedure Duration in Women Undergoing Dilation and Evacuation, Comparing Those Who Received Oxytocin With Those Who Received Placebo

	Oxytocin (n=82)	Placebo (n=78)	95% CI
Any intervention for bleeding	6 (7.3)	13 (16.7)	−21 to 1.9
Uterine massage	6 (7.3)	12 (15.4)	−19 to 3
Uterotonic medication	0	4 (5.1)	−11.3 to 1.0
Intrauterine tamponade	0	1 (1.3)	−5.0 to 2.5
Measured blood loss (mL)			
Intraoperative	127 (84–187)	246 (146–440)	69.1 to 169.1
Postoperative	15 (3–31)	17 (4–36)	−3.1 to 6.1
Total	152 (98–235)	317 (168–464)	71.6 to 181.5
Complications	5 (6.1)	20 (25.6)	−31.8 to −7.3
Hemorrhage (500 mL or more)*	3 (3.7)	17 (21.8)	−29.4 to −6.9
Major hemorrhage (1,000 mL or more)*	1 (1.2)	8 (10.3)	−17.4 to −0.7
Cervical laceration	2 (2.4)	4 (5.1)	−9.9 to 4.5
Procedure duration (min)	11.0 (8.0–14.0)	13.5 (10.0–19.0)	1.0–4.0

Data are n (%) or median (interquartile range) unless otherwise specified.
* Includes measured blood loss both intraoperatively and immediately postoperatively.

We detail procedural characteristics in Table 2. The rate of interventions to control bleeding did not differ between the oxytocin and placebo groups (7.3% vs 16.7%, difference = 9.4%, 95% CI −21.0% to 1.9%). Overall, surgeons adhered to the intervention algorithm (Box 1), most frequently using uterine massage to intervene for bleeding, followed by uterotonics, and in one case, intrauterine tamponade. One participant received just a uterotonic without massage. Total median measured blood loss was lower in the oxytocin group at 152 (interquartile range 98–235) mL compared with 3,167 (interquartile range 168–464) mL in the placebo group (95% CI 71.6–181.5). Hemorrhage (measured blood loss 500 mL or more) and cervical laceration were the only complications occurring in our sample at an overall rate of 15.6% (25/160) and were lower in the oxytocin group (6.1% vs 25.6%, difference of 19.5%, 95% CI −31.8% to 7.3%). No patients required blood transfusion, hospital transfer, or additional surgical procedures after initial D&E completion, and no uterine perforations occurred. Frequency of hemorrhage was lower in the oxytocin than placebo group (3.7% vs 21.8%, difference=18.1%, 95% CI −29.4 to −6.9%). Of those women experiencing a measured blood loss of 500 mL or more, nine (5.6%) had a total measured blood loss of 1,000 mL or more: one in the oxytocin group and eight in the placebo group (difference of 9.3%, 95% CI −17.4% to −0.7%). Procedure time was shorter in the oxytocin group by less than 3 minutes (95% CI 1.0–4.0). Pain and satisfaction were similar between groups (Table 3). Satisfaction scores were overall high in all participants.

Among women who required an intervention for bleeding (Table 4), median measured blood loss was lower in the oxytocin group at 236 (interquartile range

Table 3. Pain and Satisfaction in Women Undergoing Dilation and Evacuation, Comparing Those Who Received Oxytocin With Those Who Received Placebo

	Oxytocin (n=82)	Placebo (n=78)	95% CI
VAS pain score (cm)			
Preoperative baseline	1.3 (0.3–2.8)	1.4 (0.4–3.3)	−0.3 to 0.6
Postoperative	0.8 (0–1.5)	0.7 (0.2–3.1)	0 to 0.5
Likert satisfaction score (1–5)			
Preoperative baseline	5.0 (5.0–5.0)	5.0 (5.0–5.0)	0.0
Postoperative	5.0 (5.0–5.0)	5.0 (5.0–5.0)	0.0
Need for additional postoperative pain medications	36 (43.9)	33 (42.3)	−15.1 to 18.2
Need for postoperative antiemetics	12 (14.6)	11 (14.1)	−11.6 to 12.7

VAS, visual analog scale.
Data are median (interquartile range) or n (%) unless otherwise specified.

Table 4. Characteristics of Patients Requiring Interventions to Control Bleeding in Women Undergoing Dilation and Evacuation, Comparing Those Who Received Oxytocin With Those Who Received Placebo

	Oxytocin (n=6)	Placebo (n=13)	95% CI
Site			
University of Hawaii	6 (100)	12 (92.3)	−19.0 to 34.4
University of Washington	0	1 (7.7)	
Gestational age (wk)	19 4/7±7.5 d	20 1/7±10.8 d	−15.0 to 7.0
Nulliparity	1 (16.7)	8 (61.5)	−96.9 to 7.2
BMI (kg/m^2) 30 or greater	0	2 (15.4)	−47.2 to 16.4
No. of preoperative laminaria	6.0 (6.0–7.0)	5.0 (4.0–6.0)	0.0 to 2.0
History of cesarean delivery	1 (16.7)	2 (15.4)	−46.6 to 49.2
Measured blood loss			
Intraoperative	223 (155–364)	500 (425–666)	−596.6 to −58.4
Total	236 (181–388)	552 (433–1,070)	−917.1 to −63.8
Intervention performed			
Uterine massage only	6 (100)	9 (69.2)	−6.5 to 68
Uterotonics and massage	0	3 (23.1)	−58.2 to 12
Intrauterine tamponade	0	1 (7.7)	−34.4 to 19.0
Cervical laceration	1 (16.7)	1 (7.7)	−36.4 to 54.3
Fetal demise	0	2 (15.4)	−47.2 to 16.4
Trainee involvement in procedure	3 (50)	6 (46.2)	−56.7 to 64.3
Use of general anesthesia	6 (100)	12 (92.3)	−19.0 to 34.4

BMI, body mass index.
Data are n (%), mean±SD, or median (interquartile range) unless otherwise specified.

81–388) mL compared with 552 (interquartile range 433–1,070) mL in the placebo group (95% CI −917.1 to −63.8). Uterine massage was sufficient to control bleeding in approximately 80% (15/19, 95% CI 60.0–90.0%) of the instances that providers needed to perform an intervention. Surgeons used uterotonics, uterine tamponade, or both to control bleeding only in the placebo group.

DISCUSSION

Prophylactic use of oxytocin during D&E at 18–24 weeks of gestation did not decrease the rate of interventions used to control excess bleeding. Our 10% rate of interventions was lower than expected.[16] Our rate of intervention, however, appeared to be approximately consistent with our overall rate of hemorrhage.

Prophylactic oxytocin use does appear to decrease blood loss at 18–24 weeks of gestation. The measured blood loss was double the amount in the placebo group compared with the oxytocin group. Hemorrhage was higher in the placebo group. Additionally, the rate of hemorrhage of 1,000 mL or more was higher in the placebo group. Our overall rate of hemorrhage of 12.5% was higher than reported in previous D&E studies at 0.8–6.3%.[1–4] This higher rate could be due to the higher average gestational age in our trial, because trainees were involved in the majority of our procedures, or because previous studies did not accurately measure blood loss and thus underreported it. In a 2018 study by Serapio et al,[17] investigators compared estimated to measured blood loss during D&E at 16–24 weeks of gestation and reported measured blood loss of 500 mL or more at a frequency of 19%. In addition, they also found that surgeons consistently underreported blood loss, with the measured blood loss being two to three times the estimated amount.

A recent survey of US abortion providers showed that the majority routinely use prophylactic medications for bleeding during surgical abortion, and approximately 19% of these providers use oxytocin.[18] Some abortion providers hypothesize that, if oxytocin is administered before the entire fetus is removed, the uterus could contract around the calvarium, making it more difficult to remove and prolonging the procedure.[4] Our study demonstrated that procedures were shorter in the oxytocin group. Others theorize that oxytocin could increase postoperative uterine cramping, causing the patient unnecessary discomfort.[19] Participants reported no differences in pain or satisfaction scores.

Few prior studies have evaluated the effect of prophylactic oxytocin use on bleeding outcomes during second trimester abortion. A study by Nygaard et al[9] randomized women to receive 5 international units of oxytocin compared with placebo during surgical abortion up to 12 weeks of gestation. This study did not assess intraoperative bleeding, but

found no difference in measured and patient-reported postoperative bleeding up to 5 days later. In a nonrandomized study by Lauersen and Conrad,[8] women in the first trimester received prophylactic oxytocin versus ergonovine or control. Measured blood loss was higher in the control group compared with either uterotonic group. At our institution, we performed a retrospective cohort study of more than 700 women undergoing D&E at 14–26 weeks of gestation to evaluate the relationship between prophylactic oxytocin use and estimated blood loss.[20] In that study, we were unable to identify an association between prophylactic oxytocin use and excessive blood loss or other complications, however blood loss was not actually measured and, as previously mentioned, surgeons typically underestimate blood loss.

Strengths of our study include its randomized, double-blind design and recruitment at multiple clinical sites. Our methods for measuring blood loss were robust, including removal of amniotic fluid before measuring blood loss and weighing all post-procedure sanitary products. Because of these detailed measurements, we were able to document an accurate representation of intraoperative and postoperative bleeding as well as rate of hemorrhage. Our results are generalizable to a racially diverse population, including the often-underrepresented Native Hawaiian–Pacific Islander group.

Our primary outcome, rate of interventions to control excess bleeding, was a limitation of our study owing to its potentially subjective nature with sample size calculation based on limited evidence.[16] To standardize interventions, we did provide surgeons with an algorithm for management of excess bleeding. Because residents or fellows were involved in 65% of our study procedures, our results may be more generalizable to settings involving trainees or other inexperienced providers. It is unknown whether oxytocin would be beneficial in earlier second trimester procedures as our population started at 18 weeks of gestation. Although our study excluded women at an increased risk for hemorrhage owing to coagulopathy, anticoagulant use, chorioamnionitis, or suspected placenta accreta, we did include those with fetal demise. It is unclear how prophylactic oxytocin use would affect the subpopulation we excluded. Finally, our sample size of 160 women may have limited our ability to detect and draw conclusions about more rare complications such as uterine perforation or drug reactions.

In their clinical guideline on management of postabortion hemorrhage, the Society of Family Planning provides an algorithm to identify and classify women at risk for hemorrhage.[2] For those at moderate risk, including those at advanced gestational age, the Society of Family Planning recommends that "uterotonic medications be readily accessible."[2] Based on the results of our study, providers should consider using oxytocin prophylactically at 18–24 weeks of gestation to reduce blood loss and the risk for hemorrhage.

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