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Mifepristone prior to osmotic dilators for dilation and evacuation cervical preparation: A randomized, double-blind, placebo-controlled pilot study ☆,☆☆

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ABSTRACT

Objectives: To evaluate mifepristone impact on osmotic dilator placement and procedural outcomes when given 18 to 24 hours before dilator placement for dilation and evacuation (D&E) at 18 weeks 0 days to 23 weeks 6 days gestation.

Study Design: We performed a randomized, double-blind, placebo-controlled trial from April 2019 through February 2021, enrolling participants undergoing osmotic dilator (Dilapan) placement for a planned, next-day D&E. Participants took mifepristone 200 mg or placebo orally 18 to 24 hours before dilator placement. We used a gestational age-based protocol for minimum number of dilators. Our primary outcome was the proportion of participants for whom 2 or more additional dilators could be placed compared to the minimum gestational age-based standard. We secondarily evaluated cervical dilation after dilator removal in the operating room, subjective procedure ease, and complication rates (cervical laceration, uterine perforation, blood transfusion, infection, hospitalization, or extramural delivery).

Results: Of the planned 66 participants, we enrolled 44 (stopped due to coronavirus disease 2019-related obstacles), and 41 (19 mifepristone; 22 placebo) completed the study. We placed 2 or more additional dilators compared to standard in 7 (36.8%) and 3 (13.6%) participants after mifepristone and placebo, respectively ($p = 0.14$). We measured greater median initial cervical dilation in the mifepristone (3.2 cm[2.6−3.6]) compared to placebo (2.6 cm[2.2−3.0]) group, $p = 0.03$. Surgeon's perception of procedure being "easy" (8/19[42.1] vs 9/22[40.9], respectively, $p = 1.00$) and complication rate (3/19[15.8%] vs 3/22[13.6], respectively, $p = 1.00$) did not differ.

Conclusion: Our underpowered study did not demonstrate a difference in cervical dilator placement, but mifepristone 18 to 24 hours prior to dilators increases cervical dilation without increasing complications.

Implications: Mifepristone 18 to 24 hours prior to cervical dilator placement may be a useful adjunct to cervical dilators based on increased cervical dilation at time of procedure; however, logistical barriers, such as an additional visit, may preclude routine adoption without definite clinical benefit.

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1. Introduction

In 2018 data from the United States (U.S.) Centers for Disease Control and Prevention, approximately 8% of abortions in the U.S. occurred at 14 weeks or greater and 1.0% at 21 weeks or greater [1]. Complications from dilation and evacuation (D&E) procedures are 3.4 (95% CI 2.7–4.2) times more likely with procedures at 20 weeks gestation or greater compared to less than 20 weeks [2]. Although rare, serious complications with D&E procedures, such as uterine perforation and cervical laceration, occur less frequently with cervical preparation [3-5]. Accordingly, the Society of Family Planning clinical guidelines recommends the use of osmotic dilators starting at 20 weeks or more gestation with or without adjunctive medications [6].

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Randomized trials investigating adjunctive mifepristone at the time of cervical dilator placement at 20 weeks or more gestation have failed to demonstrate any benefit for improving cervical dilation or reducing perioperative complications [7-9]. Mifepristone, with a half-life of 25 to 30 hours [10], can soften and dilate the cervix by increasing glycosaminoglycans such as hyaluronic acid, collagenase activation, and tissue water content [11-13]. Based on these actions, ideal timing for mifepristone may be prior to osmotic dilator placement. This timing would potentially allow successful placement of more dilators, leading to greater dilation, and allow more time for mifepristone action prior to the D&E procedure. We present this pilot study to evaluating mifepristone administration 18 to 24 hours before dilator placement in persons planning a D&E procedure at 18 weeks 0 days to 23 weeks 6 days gestation.

2. Materials and methods

We performed a randomized, double-blind, placebo-controlled trial between April 2019 and February 2021 at a complex family planning tertiary referral institution. The University of California, Davis Institutional Review Board approved the study, and all participants gave written informed consent prior to beginning study procedures. At our institution, preoperative outpatient clinic visits typically occur 1 day prior to D&E procedures in the operating room and include ultrasonography, if not performed by licensed staff previously, review of medical history, obtaining surgical consent, and cervical osmotic dilator placement. We do not routinely provide feticidal injection and none of the enrolled participants received such an injection prior to their procedures.

Clinical coordinators receiving patient calls to schedule abortions estimated at 18 weeks or more asked patients if they would be interested in potential study participation. We screened interested patients by phone to explain study requirements, including an additional visit. We then scheduled interested patients for an outpatient clinic visit between 1 and 6 days prior to the planned preoperative visit date. At this visit, a physician completed the preoperative examination and operative consents per usual practice, after which an investigator evaluated the patient's medical history for study eligibility. We did not perform a pelvic exam unless clinically indicated for nonoperative indications. We initially included individuals at least 18 years of age and with gestational ages 20 weeks 0 days to 23 weeks and 6 days on procedure day to participate in the study. Exclusion criteria included intrauterine fetal demise, an allergy or contraindication to mifepristone (i.e., history of chronic adrenal failure or insufficiency, concurrent use of long-term corticosteroid therapy, or inherited porphyria), and any condition that the study investigator deemed may impede study participation or collection of study data. To facilitate recruitment, we modified the lower limit of the gestational age inclusion criteria to 18 weeks 0 days in September 2019 and removed the fetal demise exclusion criteria in December 2019.

The UC Davis investigational drug service (IDS) prepared the study medication containing either mifepristone 200 mg (Danco Laboratories, New York City, NY) or carboxymethyl cellulose (placebo) by over-encapsulation to ensure tablets were indistinguishable by look, taste, and smell. The IDS performed simple randomization using a computer-generated random sequence with a 1:1 ratio and dispensed study drug into sequentially numbered pill bottles. IDS maintained the randomization log to ensure allocation concealment until study completion. Participants, research staff, and surgical teams remained blinded to drug allocation unless necessary for participant safety. Enrolled participants received the next sequentially numbered study medication.

After signing informed consent, investigators obtained demographic and obstetric information, including prior cervical procedures and mifepristone use. Participants received the study drug with instructions to take the medication orally 18-24 hours prior to planned dilator placement (based on the scheduled pre-operative appointment) and a diary to record medication side effects from ingestion until the D&E. Research staff completed a reminder phone call at the time of expected study medication ingestion to participants who did not ingest the study drug at the enrollment visit.

Participants returned to their schedule pre-operative appointment during which research staff reviewed the timing of study medication ingestion and the study diary. Complex Family Planning Fellows or Family Planning Fellowship-trained Attending Faculty performed all study-related procedures including dilator placement and D&Es. Physicians inserted osmotic dilators (Dilapan-S 4-mm) until they encountered cervical resistance, consistent with expert opinion [6], with a minimum number goal per our gestational age-based standard clinic protocol (online Appendix A). If surgeons placed the minimum number of dilators easily, they attempted to place additional dilators if the cervix allowed without resistance. Participants marked their associated pain score on a 100-mm visual analog scale at the time of the fourth dilator placement with speculum in place with anchors of "no pain" and "worst pain in your life."

Participants presented to the hospital the following day for their scheduled D&E. Physicians could provide adjunctive misoprostol for cervical preparation based on the number of dilators placed per their discretion. Research staff reviewed study diaries reporting overnight pain medication use and side effects in the preoperative area. In the operating room, after osmotic dilator removal, surgeons measured the initial cervical dilation by placing ring forceps within the internal OS and gently opening to the widest diameter the cervix allowed [7]. The surgeon then measured the distance between the thumb holes at the widest point using a ruler. After removing the forceps, the study investigator opened them again outside of the patient to the same distance and measured the distance between the tips of the forceps from outer edge to outer edge as the cervical dilation. The surgeon then performed the standard D&E. Routine medications used during D&E to decrease bleeding include a cervical anesthetic with lidocaine 1% 20 mL with vasopressin 4 units of vasopressin [14] and oxytocin 30 units in 500 cc normal saline intravenously beginning with speculum placement [15]. Research staff present in the operating room documented the initial cervical dilation, ease of procedure, prediction of medication allocation, and operative interventions or complications after case completion.

Based on the hypothesis that mifepristone would permit easier placement of cervical dilators, we principally assessed the number of osmotic dilators placed, with a primary outcome of the proportion of participants with 2 or more additional dilators placed as compared to our standard protocol (online Appendix A). We chose a measure of 2 or more additional dilators because one more dilator could be a normal occurrence, but a routine finding of 2 or more dilators would indicate a measurable difference between groups. Secondary outcomes included the successful placement of the minimum number of osmotic dilators per institutional protocol, pain at dilator placement, initial cervical dilation, frequency of mechanical cervical dilation during D&E, surgeon's assessment of overall procedure ease, surgeon's prediction of medication allocation after case completion, and surgical interventions or complications from the time of study medication ingestion until discharge home after the procedure (i.e. use of $\geq$2 uterotonics, cervical laceration requiring repair, uterine perforation, blood transfusion, hospital admission, extramural delivery), and participant reported side effects after study medication ingestion and dilator placement. The primary surgeon determined ease of procedure based on a five-

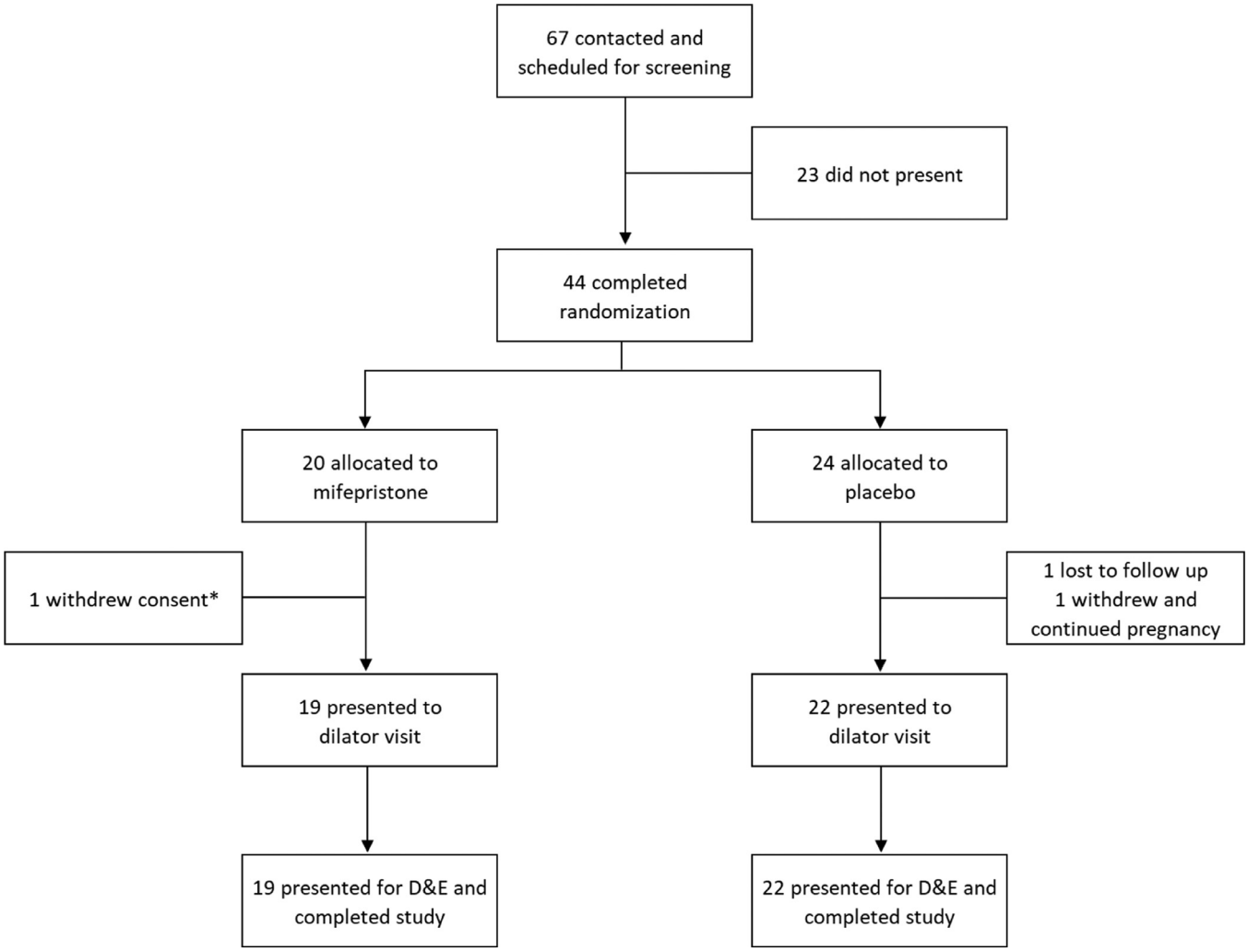

Fig. 1. Flow diagram of study participants in a randomized trial receiving mifepristone 200 mg or placebo 18 to 24 hours before cervical dilator placement for dilation and evacuation in California in 2019 to 2021.
*Participant withdrew consent prior to study drug ingestion

point scale ("Very easy," "Easy," "Moderate," "Difficult," and "Very Difficult") at case completion.

Based on the assumption that we could place 2 or more additional dilators as compared to our standard protocol in 45% of participants receiving adjunctive mifepristone and 10% of participants who did not, we estimated a sample of 60 participants for 80% power at a 5% level of significance. To account for medication non-adherence, we planned to recruit an additional 6 (10%) participants. We performed an intention-to-treat analysis using Fisher's exact test for categorical variables and Mann-Whitney U test for continuous variables, considering $p<0.05$ as significant.

3. Results

We enrolled 44 of the 66 planned participants, opting to discontinue study enrollment due to slow recruitment worsened by the coronavirus disease 2019 (COVID-19) pandemic. Figure 1 shows the study flow for the 44 participants, including three we excluded from full analysis. Of note, one participant elected to continue the pregnancy and withdrew after study medication ingestion and prior to dilator placement. For participant safety, we unblinded the randomization assignment (placebo) and notified the participant. The final data set included 41 participants who received mifepristone ($n = 19$) or placebo ($n = 22$) and completed the study. One participant (placebo) reported not ingesting the study medication; we included this participant's data for intent-to-treat analysis. Participant characteristics are presented in Table 1. We did not enroll any participants experiencing fetal demise and no participants received adjunctive misoprostol. The primary surgeon for procedures were Complex Family Planning Fellows ($n = 31$ [75.6%]) or Family Planning Attendings ($n = 10$ [24.4%]).

Although more mifepristone than placebo participants received 2 or more additional dilators compared to our standard protocol (7 [36.8%]) and 3 [13.6%], respectively), the difference was not significant ($p = 0.14$). Table 2 presents dilator placement and procedure-related secondary outcomes. We measured greater median initial cervical dilation in the mifepristone (3.2 cm [IQR 2.6-3.6]) compared to placebo (2.6 cm [IQR 2.2-3.0]) group, $p = 0.03$. After D&E case completion, the primary surgeon correctly predicted 79% (15/19) and 76% (16/21) of participants' study allocations as mifepristone and placebo, respectively ($p = 1.0$). The overall proportion of participants experiencing complications did not differ between the 2 groups; of note, most complications that occurred during the study were cervical lacerations. The six participants with lacerations included 3 in each group. One participant in the placebo group required high cervical balloon tamponade placement, blood transfusion, and hospital admission secondary to the cervical laceration. Detailed characteristics of the characteristics of

Table 1
Baseline characteristics of participants in a randomized trial receiving mifepristone 200 mg or placebo 18 to 24 hours before cervical dilator placement for dilation and evacuation in California in 2019 to 2021

Characteristic	Total $N = 41$	Mifepristone $n = 19$	Placebo $n = 22$	p-value
Age (years)	27 (24.0-31.5)	27 (24.0-32.0)	27.5 (21.0-30.5)	0.92
BMI (kg/m^2)	28.9 (24.3-32.4)	29.1 (26.4-32.6)	27.9 (23.3-32.7)	0.29
Obstetrical history				
Nulliparous	12 (29.3)	5 (26.3)	7 (31.8)	0.74
History of vaginal delivery	22 (53.7)	11 (57.9)	11 (50.0)	0.76
History of cesarean delivery	17 (41.5)	8 (42.1)	9 (40.9)	1.0
History of cesarean deliveries only	7 (17.1)	3 (15.8)	4 (18.2)	1.0
Gestational age on procedure day	21w3d (20w3d-22w6d)	21w4d (20w6d-22w5d)	21w1d (20w0d-23w1d)	0.22
18w0d – 19w6d	6 (14.6)	1 (5.3)	5 (22.7)	0.26
20w0d – 21w6d	20 (48.8)	11 (57.9)	9 (40.9)	
22w0d – 23w6d	15 (36.6)	7 (36.8)	8 (36.4)	
History of cervical procedure	2 (4.9)	1 (5.3)	1 (4.5)	1.0
Race				
White	18 (43.9)	7 (36.8)	11 (50.0)	0.53
Black	12 (29.3)	7 (36.8)	5 (22.7)	0.49
Mixed or other	10 (24.4)	4 (21.0)	6 (27.3)	0.73
Decline to identify	1 (2.4)	1 (5.3)	0	0.46
Hispanic ethnicity	9 (21.9)	4 (21.0)	5 (22.7)	1.0
High school diploma or less	19 (46.3)	9 (47.4)	10 (45.4)	1.0
Married, current	5 (12.2)	2 (10.5)	3 (13.6)	1.0

Data shown as median (interquartile range) or n (%).
BMI: body mass index; w: weeks; d: days

Table 2
Outcomes in participants in a randomized trial receiving mifepristone 200 mg or placebo 18 to 24 hours prior to cervical dilator placement for dilation and evacuation in California in 2019 to 2021.

Outcome	Total $N = 41$	Mifepristone $n = 19$	Placebo $n = 22$	p-value
Dilator visit				
Placed expected dilators or more[a]	38 (92.7)	17 (89.5)	21 (95.4)	0.59
Pain with dilators (cm)	2.9 (0.4-6.1)	1.2 (0-6.6)	3.3 (0.6-6.1)	0.67
Dilation and evacuation procedure				
Initial dilation (cm)	2.7 (2.3-3.4)	3.2 (2.6-3.6)	2.6 (2.1-3.0)	0.03
Mechanical dilation required	6 (14.6)	2 (10.5)	4 (18.2)	0.67
Ease of procedure				
Easy or very easy	17 (41.5)	8 (42.1)	9 (40.9)	1.0
Difficult or very difficult	7 (17.1)	3 (15.8)	4 (18.2)	1.0
Complications				
≥2 uterotonics	1 (2.4)	0 (0)	1 (4.5)	1.0
Cervical lacerations	6 (14.6)	3 (15.8)	3 (13.6)	1.0

Data shown as median (interquartile range) or n (%).
w: weeks; d: days
[a] Expected number of dilators based on gestational age (Online Appendix A). Three total participants did not have expected number of dilators placed: one fewer dilator at 21 (mifepristone), 21 (mifepristone), and 18 (placebo) weeks gestation.

the participants with lacerations is included in online Appendix B. Participant-reported side effects did not differ between mifepristone and placebo groups after medication ingestion or after dilator placement (Table 3).

4. Discussion

In this study, mifepristone 18 to 24 hours prior to cervical dilator insertion did not increase the ability to place additional cervical dilators; however, our study was underpowered for this primary outcome due to stopping recruitment early. While we anticipated potential clinical benefit with mifepristone use prior to cervical dilator placement given the greater cervical dilation at initiation of D&E, ease of the procedure did not differ between groups. Our limited data on complications revealed no difference between the groups. Our overall cervical laceration rate of 15% is notable. Goldberg et al. [7] reported outcomes from participants randomized to cervical dilators alone or with mifepristone on the day before the procedure, or dilators with adjunctive misoprostol on the procedure day at 16 or more weeks gestation. Cervical laceration rates ranged from none in the 99 and 100 participants receiving dilators plus mifepristone or misoprostol, respectively, and 3% (3/99) in the dilator-only group. Drey et al [16] reported a laceration rate similar to ours in a group of 196 participants at 21 to 23 weeks gestation randomized to laminaria plus placebo or laminaria plus misoprostol on the procedure day, with rates of 13% with adjunctive misoprostol and 6% with placebo. Overall, the denominators from these studies and ours are too small and characteristics between studies are quite different such that identifying potential cervical laceration risk predictors is not appropriate. For example, our study population included many participants with prior cesarean deliveries (41.5%) and gestations 20 weeks and over (85%). We also involved trainees as the primary surgeon in 75.6% of procedures. All of these factors significantly increase the risk of cervical lacerations and other surgical complications [8, 17].

A prior large randomized controlled trial by Goldberg and colleagues [7] suggests that adjunctive mifepristone at time of cervical dilator placement 1 day prior to D&E shortens procedure time and reduces the procedural difficulty, especially for procedures performed at 19 weeks or greater. Our finding differs from these re-

Table 3
Participant-reported side effects in a randomized trial after mifepristone 200 mg or placebo medication ingestion and cervical dilator placement prior to dilation and evacuation in California in 2019 to 2021

Side effects[a]	After medication ingestion			After dilator placement		
	Mifepristone $n = 19$	Placebo $n = 22$	p-value	Mifepristone $n = 19$	Placebo $n = 22$	p-value
Cramping	8 (42.1)	4 (18.2)	0.17	19 (100)	21 (95.4)	1.0
Bleeding	1 (5.3)	0 (0)	0.46	13 (68.4)	15 (68.2)	1.0
Nausea	5 (26.3)	3 (13.6)	0.44	11 (57.9)	7 (31.8)	0.12
Vomiting	0 (0)	0 (0)	1.0	7 (36.8)	6 (27.3)	0.74
Weakness	3 (15.8)	1 (4.5)	0.32	6 (31.6)	7 (31.8)	1.0
Dizziness	2 (10.5)	2 (9.1)	1.0	2 (10.5)	6 (27.3)	0.25
Fatigue	2 (10.5)	1 (4.5)	0.59	3 (15.8)	5 (22.7)	0.70
Headache	2 (10.5)	2 (9.1)	1.0	2 (10.5)	1 (4.5)	0.59
Fevers or chills	0 (0)	0 (0)	1.0	1 (5.3)	3 (13.6)	0.61
Diarrhea	0 (0)	0 (0)	1.0	2 (10.5)	0 (0)	0.21

Data shown as n (%).
[a] Side effects as reported on participant diaries; none reported as severe, and no additional evaluations or management required.

sults. While this may be a result of the small sample size, it also suggests that cervical preparation with optimal cervical dilation is only one of several factors that determine the ease or difficulty of D&E procedures [7,16–18].

The strength of this study is its randomized double-blind, placebo-controlled design. Cervical preparation with osmotic dilators vary among providers and institutions by natural and synthetic types and we utilized a standard protocol of the same size and type of dilators to remove this variability. As placement of cervical dilators could be a subjective process and not easily generalizable to other clinical sites, we also obtained data on several secondary outcomes. Limitations include our small sample size as we were underpowered to evaluate the primary outcome. While D&E procedure safety is an important clinical outcome, we relied on measurements of cervical preparation as proxy due to the rarity of complications.

Adjunctive mifepristone at time of dilator placement is well tolerated [7,8] and demonstrates potential benefits during D&E procedures [7]. Our study, which uniquely assessed possible benefits of mifepristone for cervical dilator placement and concurrently the longer action of mifepristone prior to D&E, attempted to further identify clinical evidence of improvement. Mifepristone use prior to cervical dilator insertion may provide clinical benefit by allowing for 2 days of action, as evidenced by the greater cervical dilation at time of D&E procedure; however, a sufficiently powered study would be necessary to provide more conclusive evidence. Mifepristone administration the day prior to dilator placement is hindered by the Risk Evaluation and Mitigation Strategy (REMS) program, which requires in-person mifepristone dispensing by a clinician. Access to abortion services, especially during the second trimester, becomes more challenging with logistical barriers in planning and distance from experienced clinicians [19,20]. With the current study design, participation in this study required an additional visit to the clinic and attending 3 visits for a D&E procedure was not feasible for many patients who traveled far distances to obtain our referral services. Should future research demonstrate clinical benefit of mifepristone prior to dilators, involving a facility closer to the patient for preoperative evaluation and removal of the mifepristone REMS program to enable outpatient prescribing of mifepristone could decrease travel burden and increase access to safe D&E.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.contraception.2021.08.013.

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