Mifepristone prior to osmotic dilators for dilation and evacuation cervical preparation:

A randomized, double-blind, placebo-controlled pilot study

Clinicaltrials.gov: NCT03714880

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1.1 Design methodology

1.1.1 Research design and general methodological approach

The planned research design is a double-blind, placebo-controlled randomized trial.

A. Study arm: mifepristone 200 mg orally 18-24 hours prior to osmotic dilator placement
B. Control arm: placebo oral medication 18-24 hours prior to osmotic dilator placement

The total number of women will be 66 and 33 women will be allocated to each group (Appendix – CONSORT Flow Diagram).

1.1.2 Criteria for the selection of subjects

Inclusion criteria:

A. Women planning dilation and evacuation with cervical dilator placement at gestational ages 20 weeks 0 days to 23 weeks 6 days on procedure day
B. English-speaking/writing

Exclusion criteria:

A. Allergy to mifepristone
B. Any condition that in the opinion of the investigator could impede study participation or collection of study data

1.1.3 Subject recruitment and allocation

<u>Participant identification</u>

Potential participants will be identified either at time of referral to UC Davis Family Planning Center from outside clinics after dating ultrasound is performed or when presenting directly for dating ultrasound at UC Davis Family Planning Center.

<u>Pre-visit phone call</u>

For women who have been referred to UC Davis and have already had a dating ultrasound, research staff will call to explain the study. For women not interested in the study, a standard pre-operative visit per clinic guidelines will be scheduled. For women who are

interested in enrolling in the study, a screening and enrollment visit with be scheduled. Women will be notified that they will be randomly allocated to mifepristone or placebo medication.

1.1.4 Description of the drugs and devices to be studied

Mifepristone exerts anti-progestin activity by binding with high affinity to progesterone receptors and causing an increase in glycosaminoglycans, such as hyaluronic acid, increases collagenase activation and tissue water content [14-17]. These actions promote softening and dilation of the cervix [14,15] and also increase the myometrial response to exogenous prostaglandins, such as misoprostol [17].

1.1.5 Admission procedure

Day 1: Screening and Enrollment

This visit is scheduled after a pre-visit phone call or at the time of the dating ultrasound visit. Pre-operative examination and operative consents will be reviewed and signed per usual practice. Research staff will review the study and obtain informed consent for the study. Office or formal radiologic ultrasounds will be performed based on clinical indication. Study medication will then be dispensed with instructions to take 18-24 hours prior to scheduled pre-operative visit. All women will receive a diary to collect side effect information.

Day 2: Pre-operative visit

Women will return for their scheduled pre-operative visit the day prior to their scheduled procedure. Diaries will be collected and reviewed and osmotic dilators (Dilapan-S 4-mm) will be placed. Pain score measured by VAS will be collected at time of dilator placement.

Day 3: Standard dilation and evacuation procedure

Participants will proceed to the operating room and undergo sedation per anesthesia guidelines. Initial cervical dilation using Pratt dilators will be measured after dilator removal. Standard dilation and evacuation will be performed.

1.1.6 Follow-up procedure

There will be no follow-up necessary and the end of the procedure will indicate study completion.

1.1.7 Criteria for discontinuation

Women who report not taking the study medication will be discontinued from the study. Participants may discontinue from the study for any reason.

1.1.8 Laboratory and other investigations

Not applicable

1.1.9 Data management

Each participant will be assigned a file in a locked cabinet of a locked office. Participant files will contain signed consent forms, study allocation number, and paper copies of data collection forms.

1.1.10 Data analysis

As the primary outcome is a dichotomous variable, I will perform logistic regression analyses. The number of cervical dilators will be collected either at time of clinic visit or by chart review. Missing data will be minimized by allowing for exclusion of any potential participant who may be judged to have increased risk for loss to follow up at time of enrollment and prior to randomization. We will include all women randomized and perform intent-to-treat analysis with no apparent exclusions. In addition, a second analysis will be conducted excluding women who do not report ingesting the study medication.

At time of enrollment, we plan to collect baseline demographic data, including age, race, ethnicity, education level, obstetric history, and history of cervical procedures. I will perform univariate analyses to compare the two study groups at baseline. If any variables are significantly different, I will utilize those variables to adjust the logistic regression for the primary outcome. While not powered to detect a statistically significant difference among the two groups for the secondary outcomes, exploratory analyses will be performed to identify possible trends and areas of interest for a subsequent larger trial. The data analysis will be as follows:

Secondary outcome	Data analysis plan
Proportion of appropriate number of dilators	Logistic regression
Cervical dilation at time of procedure	Linear regression
Number of tablets of ibuprofen and Tylenol #3 utilized with dilators in place	Logistic regression
Proportion of women requiring mechanical dilation at time of procedure	Logistic regression
Pain at time of dilator placement (VAS)	Linear regression
Provider perception of overall ease of procedure Provider perception of difficulty in dilating the cervix when required	Logistic regression
Overall complication and adverse event rate	Logistic regression

1.1.11 Number of subjects and statistical power

	Control group

	% with +2 dilators	1	5	10	15	20
Study group	10	242	950	--	--	--
	20	100	176	438	1864	--
	30	60	86	144	268	632
	35	50	68	102	166	304
	40	42	54	76	114	182
	45	36	44	**60**	84	124
	50	30	38	50	66	90
	60	24	28	34	44	56
	70	18	22	26	30	38
	80	14	16	20	22	26

The appropriate number of dilators is based on gestational age at this university:

a. 20 weeks 0 days to 20 weeks 6 days: at least 5 dilators
b. 21 weeks 0 days to 21 weeks 6 days: at least 6 dilators
c. 22 weeks 0 days to 23 weeks 6 days: at least 7 dilators

Without adjunctive medications, it is assumed that placing two more than the standard number of dilators will be difficult and a rare occurrence in about 10% of women. With adjunctive preparation with mifepristone, dilator placement will lead to an increased proportion of women (45%) receiving two additional dilators than the indicated number. We require 60 participants to detect a difference of 35% between the two groups and maintain 80% power and an alpha of 0.05. To account for medication nonadherence, we plan to recruit 10% more patients for a total of 66 women.