STUDY PROTOCOL
Uterotonic prophylaxis after D&E

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Study Design

We propose a three-arm randomized, double-blinded, placebo-controlled trial of intramuscular MM versus rectal misoprostol versus placebo after D&E to evaluate the effect of prohylaxis on excessive bleeding. All English- or Spanish- speaking women undergoing D&E at San Francisco General Hospital's Women's Options Center (SFGH WOC) between 20 weeks' 0 days' and 24 weeks' 0 days' gestation will be eligible for recruitment. Women will be excluded if they have a pre-operative diagnosis of hypertension, are using protease inhibitors, have known coagulopathy or history of obstetric hemorrhage requiring blood transfusion, placenta accreta, increta or percreta, and any other contraindication to MM or misoprostol use.

Study Procedures

Recruitment: All eligible women will be identified on the pre-operative day by the research assistant, after clinical staff performs an ultrasound to determine the gestational age. For most women, the pre-operative day is one day prior to the D&E. For a minority of women, it is two days prior to the D&E. After eligibility is confirmed, the research assistant will approach the patient prior to dilator placement to explain the study, and obtain consent.

Randomization: On the day of the D&E, women who consented to participate in the trial will be assigned a study number and random assignment to one of three study arms will be made. We plan to use block randomization for two gestational age ranges (1) 20 weeks 0 days to 22 weeks 0 days; (2) 22 weeks 1 day to 24 weeks 0 days. We plan to use a random number table to assign each study number to one of three arms. By randomizing women just prior to the D&E, we will minimize any negative effect on the randomization scheme if women either fail to return for the procedure or withdraw consent prior to the D&E.

Blinding: MM and saline syringes (placebo) will be prepared by the SFGH Pharmacy. Misoprostol tablets and placebo tablets will be prepared by Abbott Laboratories. The MM and placebo syringes will be identical as will the misoprostol and placebo tablets. No clinical providers or research staff will have access to the randomization scheme. Each subject will receive an intramuscular injection and placement of rectal tablets without knowledge of their contents. To assess the quality of blinding, providers will be asked by the research assistant at the end of the procedure to which group they thought a study patient was assigned.

D&E providers: Ten faculty members at SFGH do D&Es at SFGH WOC. All are routine and experienced providers. D&Es are also done by a rotating third-year resident and a first- or second-year family planning fellow. For the purposes of this trial, only faculty members or the second-year family planning fellow will be performing the D&E.

Reimbursement: Women will be given a $15 gift card for participating in the trial.

Intervention

Women in this trial will be randomized to one of three arms: (1) MM 0.2 mg intramuscular injection and placebo rectal misoprostol, (2) saline (placebo) intramuscular injection and misoprostol 800 mcg rectal, (3) saline (placebo) intramuscular injection and placebo rectal misoprostol at the completion of the D&E. Completion will be defined as immediately after the last suction. At SFGH WOC, it is standard procedure for providers to perform a final suction at the completion of the procedure. Once the provider states that she/he is finished with the last suction, the nurse will administer the intramuscular injection. The assigned tablets will be given to the provider to place rectally. All study drugs and placebos will be prepared identically and labeled as, “Study drug”.

Outcomes

Primary outcome: Our primary outcome of excessive bleeding will be measured with a composite outcome that includes measured post-operative blood loss greater than 125 cc or specific interventions done to manage the excessive bleeding (Table 1). Only one of the listed criteria is needed to qualify as a positive outcome. In addition to our primary, composite outcome, we will also record the number of interventions performed for what the provider deems excessive uterine bleeding. We plan to do sensitivity analyses as follows: (1) a dichotomous outcome of 2 or more interventions used versus less than 2; (2) excluding administration of uterotonics and uterine pressure.

We are not aware of any literature measuring blood loss after D&E at 20 to 24 weeks’ gestation. In our clinic, we have observed that approximately 95% of women within this gestational age range have a total post-operative blood loss to be less than 125 cc. We are thus considering greater than 125 cc post-operative blood loss to be indicative of excessive bleeding, and thus have included it as one of the criteria for our composite outcome. For uterotonic medications administered or prescribed, we will record the type (misoprostol, hemabate, MM), dosage, and number of doses.

Many cases of excessive bleeding will fulfill more than one criterion listed in Table 1. For example, most women given a prescription for a uterotonic medication at discharge will likely have received a uterotonic medication. In addition, most women with > 125 cc blood loss post-operatively will likely have received at least one uterotonic medication. In order to increase our sensitivity in detecting excessive bleeding, we have included all possible criteria, and will record the number of interventions someone received. Providers who wish to give a uterotonic medication to treat excessive bleeding will be instructed to wait 5 min after the study drug has been given. They will be able to choose any uterotonic as they normally would.

Table 1. Clinical factors included in composite outcome of excessive bleeding after D&E.

Total blood loss > 125 cc (after D&E)
Transfusion
Admission for bleeding
Re-aspiration for bleeding
Balloon tamponade
Uterine artery embolization
Major surgery for bleeding
At least 1 uterotonic medication given
Prescription given for any uterotonic medication at discharge
Uterine compression (uterine massage or manual pressure for 2 minutes

Secondary outcome: A secondary outcome will be overall blood loss after the D&E. Blood loss will be measured from the start of the procedure, defined as removal of cervical dilators, to the end of the procedure (after last suction). All bleeding that occurs after last suction will be considered post-operative bleeding. Blood loss will be measured by collecting the blood in a draped bag underneath the patient and by weighing all gauze used during the procedure. To assess post-procedure blood loss in the recovery room, we will also weigh pads and chux from the time of last suction to discharge, then converting grams into milliliters using the specific gravity of blood which is 1.06 grams per milliliter (Figure 1). We will compare mean total blood loss volume (TBLV) after D&E, a continuous outcome, among the three arms. We have successfully piloted this method of measuring blood loss in our clinic.

Figure 1. Measuring total blood loss after D&E

TPW (grams)	Total pad weight = weight of all pads used
TBLW (grams)	Total blood loss weight = Total pad weight – (Dry pad weight * # of pads)
TBLV (milliliters)	Total blood loss volume = Total blood loss weight / 1.06 g/mL