Misoprostol Effect on Second Trimester Abortion Blood Loss

Study Protocol

NCT06078501

August 23, 2023

Title: Misoprostol Effect on Second Trimester Abortion Blood Loss
Investigators: Simranvir Kaur, MD; Kate Shaw, MD, MS

Non-technical summary:
Although serious complications from second trimester abortion are rare hemorrhage is the most common cause of procedural abortion related morbidity and mortality (Zane et al., 2015). Misoprostol is a prostaglandin E1 analogue that is used by 75% of clinicians (White et al., 2018) prior to procedural abortion for the purpose of cervical preparation. Misoprostol is also known to decrease blood loss in first trimester abortion and is used to treat postpartum hemorrhage, however the effect of preprocedural misoprostol on second trimester abortion blood loss is not well described.

We will conduct a double blinded placebo-controlled gestational age stratified superiority trial of those undergoing procedural abortion between 18 and 23 weeks gestation at Stanford Health care. Participants will be randomized to either 400mcg buccal misoprostol or placebo on the day of the procedure. A quantified blood loss (QBL) will be measured during the procedure and participants will complete a survey to assess symptoms. Our primary outcome is quantified blood loss. Secondary outcomes include clinical interventions to manage excess bleeding, total procedure time, provider reported experience, patient reported experience. We plan to recruit 80 subjects powered to detect a 30% reduction in QBL in those who received misoprostol compared to the control group.

This study has the potential to increase the safety of an already safe procedure and establish clinical benefits of choosing misoprostol as an agent for cervical preparation.

Specific Aims:
Primary aim:
To investigate the impact of administering 400 micrograms of buccal misoprostol 90-120 minutes prior to second trimester procedural abortion on quantified blood loss.

Secondary aims:
Patient experience: evaluate the subjective experiences of patients who receive misoprostol before second trimester abortion focusing on pain before and after administration of the treatment, side effects, and overall satisfaction with the experience.

Procedure: analyze whether the use of misoprostol prior to second trimester abortion influences the procedure times, ease of procedure, provider estimated blood loss, provider satisfaction with cervical preparation, and whether the clinician could tell whether misoprostol was used.

Background and Significance:
The definition of hemorrhage in second trimester abortion varies across studies with some focusing on volume of blood loss whereas others focus on clinical outcomes or interventions related to blood loss. Given these variable definitions the incidence of hemorrhage ranges from 0.9 to 10 per 1000 cases (Altman et al., 1985; Castleman et al., 2006; Frick et al., 2010; Patel et al., 2006; Schulz et al., 1985).

Clinical guidelines from the Society of Family Planning (SFP) recommend adequate cervical preparation and to consider vasopressin in a paracervical block to prevent hemorrhage for all patients (J. Kerns & Steinauer, 2013). The same guidelines outline management of hemorrhage including uterine massage, uterotonic medications, re-aspiration, balloon tamponade, uterine artery embolization, and hysterectomy. A randomized controlled trial (RCT) in 2019 by Whitehouse et. Al. examined the effects of prophylactic oxytocin on blood loss during procedural abortion 18-24w duration with primary outcome of frequency of interventions to control excess bleeding(Whitehouse et al., 2019). While prophylactic oxytocin did not decrease interventions needed to control excess bleeding, it did decrease hemorrhage (defined as blood loss of 500mL or more) by 18% (95% CI -29 to -6.9) and median blood loss by 165mL (152mL in oxytocin group [interquartile range 98-235] versus 317mL [interquartile range 168-464; 95% CI 71.6-181.5]). Another RCT by Kerns in 2021 examined the effects of prophylactic intramuscular methylergonovine for people undergoing procedural abortion 20-24 weeks (J. L. Kerns et al., 2021). They found no improvement in the composite of indicators of excessive blood loss with a paradoxical increase in the number of individual excessive bleeding outcomes for the group that received methylergonovine.

Misoprostol is a synthetic prostaglandin E1 analogue that is used in gynecologic, obstetric, and abortion care to induce uterine contractions and for cervical softening (Allen & O'Brien, 2009). It has been shown to overall decrease estimated blood loss in first trimester procedural abortion (Ngai et al., 1995, 1999; Saxena et al., 2003; Vimala et al., 2003) and is used to treat postpartum hemorrhage ("Practice Bulletin No. 183: Postpartum Hemorrhage," 2017). Cervical

preparation is required prior to second trimester procedural abortion and can be broadly understood in two different categories: mechanical and pharmacologic. Mechanical methods of cervical preparation include inserting osmotic dilators (Dilapan-S or laminaria tents) or transcervical balloons (foley balloon or Cook balloon). Pharmacologic methods of cervical preparation include mifepristone, misoprostol, and ulipristal acetate. Misoprostol is commonly used as part of cervical preparation for second trimester abortion (Diedrich et al., 2020; Fox & Krajewski, 2014) with 75% of clinicians report using misoprostol (White et al., 2018) it has not been shown to be a superior method of cervical preparation nor has it shown to improve clinical outcomes. The impact of use on procedural blood loss has not been consistently described (Cahill et al., 2020). Studies that do report on blood loss tend to use estimated blood loss which has been shown to consistently underestimate blood loss when compared to a measured blood loss (Serapio et al., 2018). Some clinicians do not use misoprostol out of concern for unpleasant side effects, how the procedure is then performed, and impact on procedural times (Drey et al., 2014). Further studies examining the specific effects of misoprostol on blood loss could help to better inform clinicians on the impact of misoprostol for cervical preparation on bleeding with second trimester procedural abortion.

Project Design and Methods:

Study Location

Patients will be recruited at Stanford Gynecology Clinic in Palo Alto, CA. Stanford University is a large tertiary care center with patients referred from the seven Perinatal Diagnostic Centers (PDCs) across Northern California with fetal anomalies as well as local independent clinics.

Research Design and General Methodological Approach

The proposed study is a conduct a randomized, double-blinded, placebo-controlled, superiority trial. Participants will be consented and randomized using a computer-generated random number producing algorithm to receive either misoprostol 400mcg or placebo, buccally 90-120 minutes prior to their scheduled procedure time. Pharmacy staff filled identical, opaque pill containers with either two 200mcg misoprostol tablets or two 50-mg vitamin B6 tablets (placebo) because no identical appearing placebo exists for misoprostol. To ensure blinding of research and clinical staff subjects will self-administer study tablets in private where a research assistant who is uninvolved with collection of data will be available to assist patients with correct buccal placement. All other clinical and research staff will be blinded to the study group assignments until data analysis is complete.

The primary outcome will be proportion of participants with blood loss (QBL) above published medians by gestational duration(Serapio et al., 2018). To detect a 30% reduction in the proportion of participants with QBL greater than the median, with an alpha of 0.05 and a power of 80%, we would need 36 participants per group. Accounting for drop out, loss to follow up, and missing data, we plan to recruit 40 per group, for a total of 80 participants. With an estimated 180 procedures per year, 80% eligible, and 60% enrollment, we estimate the study will take 12-15 months to enroll. QBL will be measured using previously published protocols(Serapio et al., 2018). QBL was selected as the primary outcome because the incidence

of hemorrhage in second trimester abortion is a rare outcome. Lower QBLs correspond to lower risks and rates of hemorrhage therefore QBL may be a reasonable proxy to understanding morbidity and mortality related to procedural second trimester abortion.

Secondary outcomes will include clinical intervention to manage excess bleeding (use of uterotonics, uterine artery embolization, uterine balloon tamponade, blood transfusion, hysterectomy), total procedure time, provider-reported experience (ease of procedure, provider estimated blood loss, provider satisfaction with cervical dilation, and whether the clinician accurately predicted which treatment arm the subject was in), participant-reported experience (pain, side effects: nausea, vomiting, diarrhea, fevers), preoperative exam for dilation, need for mechanical dilation. Patient and provider experience are important outcomes to consider as some providers specifically chose methods of cervical preparation based on patient experiences and based on the way that the provider themselves perform the procedure. Because there is no one standard way to prepare cervices for second trimester procedural abortion providers choose methods of cervical preparation that they are most comfortable and familiar with based on how it changes the way they perform the procedure itself and how patients tolerate the various methods of cervical preparation. For example, pharmacologic preparation with misoprostol may cause side effects such as nausea, diarrhea, and fever, whereas osmotic dilators may cause more pain with placement and more pain overnight prior to procedure.

Criteria for Selection of Subjects
Inclusion: Pregnant people, 18 years of age or older; intrauterine pregnancy between 18/0-23/6 weeks of gestational age (by ultrasound dating performed prior to same day of enrollment visit) consented for an induced abortion; English or Spanish speaking, able to consent for a research study, literate in English or Spanish.

Exclusion: known coagulopathy, suspected morbidly adherent placenta spectrum, multiple gestation, current infection, ruptured membranes, or fetal demise at time of enrollment.

Subject Recruitment and Allocation
Subjects will be recruited from Stanford Gynecology Clinic on the day of their Family Planning consultation, after consent for, but prior to abortion. Only patients in the appropriate gestational ages will be approached. Potential participants will be screened for the study and if eligible and willing to participate in the project they will be consented for the study.

Description of Drugs and Devices
Misoprostol is a prostaglandin E1 analogue with two FDA labeled indications: 1. prevention of nonsteroidal anti-inflammatory drug-induced gastric ulcers and 2. Termination of intrauterine pregnancy through 70d gestation in combination with mifepristone. Various off label uses exist in obstetric, gynecologic, and abortion care including cervical preparation and labor induction, early pregnancy loss, incomplete abortion, postpartum hemorrhage (prevention/treatment), termination of intrauterine pregnancy as monotherapy.

Data Management & Analysis

Stanford University has a license for the RedCap data management system(Harris et al., 2009). RedCap is a web-based application that is secure, reliable, and HIPAA-compliant for strong research study data. RedCap is designed with build-in features to address confidentiality and compliance requirements. Electronic surveys will be administered via study iPad on the day of the procedure. Data associated with patient health identifiers (PHI) including the signed informed consent will be collected electronically. RedCap allows for easy data download into SAS or other statistical software programs. No data will be collected on paper forms. SAD OnDemand will be used for data analysis. Data will be analyzed with parametric or non-parametric statistical tests, as appropriate.

Summary

Second trimester procedural abortion is safe. The uncommon experiences of morbidity and mortality are often from excessive blood loss. Misoprostol is a medication commonly used prior to second trimester abortion for cervical preparation. This study will investigate whether misoprostol influences second trimester procedural abortion blood loss. This trial represents an opportunity to improve patient outcomes during an otherwise difficulty, often stigmatized, reproductive event.

Allen, R., & O'Brien, B. M. (2009). Uses of misoprostol in obstetrics and gynecology. *Rev Obstet Gynecol*, *2*(3), 159–168.

Altman, A. M., Stubblefield, P. G., Schlam, J. F., Loberfeld, R., & Osathanondh, R. (1985). Midtrimester abortion with Laminaria and vacuum evacuation on a teaching service. *J Reprod Med*, *30*(8), 601–606.

Cahill, E. P., Henkel, A., Shaw, J. G., & Shaw, K. A. (2020). Misoprostol as an adjunct to overnight osmotic dilators prior to second trimester dilation and evacuation: A systematic review and meta-analysis(). *Contraception*, *101*(2), 74–78. https://doi.org/10.1016/j.contraception.2019.09.005

Castleman, L. D., Oanh, K. T., Hyman, A. G., Thuy le, T., & Blumenthal, P. D. (2006). Introduction of the dilation and evacuation procedure for second-trimester abortion in Vietnam using manual vacuum aspiration and buccal misoprostol. *Contraception*, *74*(3), 272–276. https://doi.org/10.1016/j.contraception.2006.03.021

Diedrich, J. T., Drey, E. A., & Newmann, S. J. (2020). Society of Family Planning clinical recommendations: Cervical preparation for dilation and evacuation at 20-24 weeks' gestation. *Contraception*, *101*(5), 286–292. https://doi.org/10.1016/j.contraception.2020.01.002

Drey, E. A., Benson, L. S., Sokoloff, A., Steinauer, J. E., Roy, G., & Jackson, R. A. (2014). Buccal misoprostol plus laminaria for cervical preparation before dilation and evacuation at 21-23 weeks of gestation: A randomized controlled trial. *Contraception*, *89*(4), 307–313. https://doi.org/10.1016/j.contraception.2013.10.013

Fox, M. C., & Krajewski, C. M. (2014). Cervical preparation for second-trimester surgical abortion prior to 20 weeks' gestation: SFP Guideline #2013-4. *Contraception*, *89*(2), 75–84. https://doi.org/10.1016/j.contraception.2013.11.001

Frick, A. C., Drey, E. A., Diedrich, J. T., & Steinauer, J. E. (2010). Effect of prior cesarean delivery on risk of second-trimester surgical abortion complications. *Obstet Gynecol*, *115*(4), 760–764. https://doi.org/10.1097/AOG.0b013e3181d43f42

Harris, P. A., Taylor, R., Thielke, R., Payne, J., Gonzalez, N., & Conde, J. G. (2009). Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support. *Journal of Biomedical Informatics*, *42*(2), 377–381. https://doi.org/10.1016/j.jbi.2008.08.010

Kerns, J. L., Pearlson, G., Mengesha, B., Harter, K., Jackson, R. A., & Drey, E. A. (2021). A randomized controlled trial of methylergonovine prophylaxis after dilation and evacuation abortion. *Contraception*, *103*(2), 116–120. https://doi.org/10.1016/j.contraception.2020.10.009

Kerns, J., & Steinauer, J. (2013). Management of postabortion hemorrhage: Release date November 2012 SFP Guideline #20131. *Contraception*, *87*(3), 331–342. https://doi.org/10.1016/j.contraception.2012.10.024

Ngai, S. W., Chan, Y. M., Tang, O. S., & Ho, P. C. (1999). The use of misoprostol for pre-operative cervical dilatation prior to vacuum aspiration: A randomized trial. *Hum Reprod*, *14*(8), 2139–2142. https://doi.org/10.1093/humrep/14.8.2139

Ngai, S. W., Tang, O. S., Lao, T., Ho, P. C., & Ma, H. K. (1995). Oral misoprostol versus placebo for cervical dilatation before vacuum aspiration in first trimester pregnancy. *Hum Reprod*, *10*(5), 1220–1222. https://doi.org/10.1093/oxfordjournals.humrep.a136122

Patel, A., Talmont, E., Morfesis, J., Pelta, M., Gatter, M., Momtaz, M. R., Piotrowski, H., & Cullins, V. (2006). Adequacy and safety of buccal misoprostol for cervical preparation prior to termination of second-trimester pregnancy. *Contraception*, *73*(4), 420–430. https://doi.org/10.1016/j.contraception.2005.10.004

Practice Bulletin No. 183: Postpartum Hemorrhage. (2017). *Obstet Gynecol*, *130*(4), e168–e186. https://doi.org/10.1097/aog.0000000000002351

Saxena, P., Salhan, S., & Sarda, N. (2003). Role of sublingual misoprostol for cervical ripening prior to vacuum aspiration in first trimester interruption of pregnancy. *Contraception*, *67*(3), 213–217. https://doi.org/10.1016/s0010-7824(02)00517-6

Schulz, K. F., Grimes, D. A., & Christensen, D. D. (1985). Vasopressin reduces blood loss from second-trimester dilatation and evacuation abortion. *Lancet*, *2*(8451), 353–356. https://doi.org/10.1016/s0140-6736(85)92496-1

Serapio, E. T., Pearlson, G. A., Drey, E. A., & Kerns, J. L. (2018). Estimated versus measured blood loss during dilation and evacuation: An observational study. *Contraception*, *97*(5), 451–455. https://doi.org/10.1016/j.contraception.2018.01.008

Vimala, N., Mittal, S., & Kumar, S. (2003). Sublingual misoprostol for preabortion cervical ripening in first-trimester pregnancy termination. *Contraception*, *67*(4), 295–297. https://doi.org/10.1016/s0010-7824(03)00024-6

White, K. O., Jones, H. E., Shorter, J., Norman, W. V., Guilbert, E., Lichtenberg, E. S., & Paul, M. (2018). Second-trimester surgical abortion practices in the United States. *Contraception*. https://doi.org/10.1016/j.contraception.2018.04.004

Whitehouse, K., Tschann, M., Soon, R., Davis, J., Micks, E., Salcedo, J., Savala, M., & Kaneshiro, B. (2019). Effects of Prophylactic Oxytocin on Bleeding Outcomes in Women Undergoing Dilation and Evacuation: A Randomized Controlled Trial. *Obstet Gynecol*, *133*(3), 484–491. https://doi.org/10.1097/aog.0000000000003104

Zane, S., Creanga, A. A., Berg, C. J., Pazol, K., Suchdev, D. B., Jamieson, D. J., & Callaghan, W. M. (2015). Abortion-Related Mortality in the United States: 1998–2010. *Obstetrics & Gynecology*, *126*(2), 258–265. https://doi.org/10.1097/aog.0000000000000945