Cabergoline for Lactation Inhibition After Early Second-Trimester Abortion or Pregnancy Loss: A Randomized Controlled Trial

Study Protocol and Statistical Analysis Plan

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Title: Cabergoline for Lactation Inhibition after Early Second-Trimester Abortion or Pregnancy Loss: A randomized controlled trial

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Non-technical summary: Breast pain following second-trimester abortion is common. Breast engorgement and milk leakage following second-trimester perinatal loss and abortion can cause both physical pain and emotional distress. Dopamine agonists have previously been shown to be effective in lactation inhibition for third-trimester fetal/neonatal loss or contraindications to breastfeeding. Our own prior work demonstrated that compared to placebo, a single dose of cabergoline was effective in preventing breast symptoms after abortion or loss 18-28 weeks. As lactogenesis starts as early as 16 weeks gestation, we hope to determine the efficacy of cabergoline earlier in the second trimester,16-20 weeks.

We will conduct a double-blinded, placebo-controlled, gestational-age stratified superiority trial of those undergoing abortion or intrauterine fetal demise between 16 and 20-weeks gestation at Stanford Health Care. Participants will be randomized to either cabergoline 1 mg or placebo the day of procedure. Participants will complete a survey to assess symptoms, using the validated Bristol Breast Symptoms Inventory, and side-effects at baseline and Day 2, 4, 7, and 14 after the procedure. Our primary outcome is breast symptoms on Day 4 based on term lactation physiology. Secondary outcomes include satisfaction, acceptability, and side-effects. We plan to recruit 72 subjects powered to detect a 45% decrease in those reporting breast symptoms compared to the control group.

This study has the potential to improve overall patient experience by validating the routine use of cabergoline for lactation inhibition in the early second-trimester after abortion or pregnancy loss.

Specific aims

Lactogenesis is a two-stage physiologic process of developing the ability to secrete milk that starts in the 16th week of pregnancy and continues after delivery, peaking at day 4 postpartum, regardless of the birth outcome (1). Breast pain following second-trimester abortion is common (2). Breast engorgement and milk leakage following second-trimester perinatal loss and abortion can cause both physical pain and emotional distress (3). Dopamine agonists have previously been shown to be safe and effective in lactation inhibition for third-trimester fetal/neonatal loss or for those with contraindications to breastfeeding (4). Our own research recently found that among those seeking abortion care or management of fetal demise 18-28 weeks gestation, significantly fewer people who received a single dose of cabergoline reported any breast symptoms compared to placebo (5). Fewer than 1% of abortion nationally occur this late in pregnancy; most free-standing clinics provide abortion care for those less than 20 weeks. In our original study, we were underpowered to specifically make claims about those 18-20 weeks, and those 16-18 weeks were excluded. As there is biologic plausibility that lactogenesis starts as early as 16 weeks, this follow-up study seeks to determine if cabergoline is beneficial earlier in the second-trimester.

Therefore, we are hoping to answer whether cabergoline is superior to placebo at preventing symptomatic breast engorgement after early second-trimester abortion or loss. We will conduct a double-blinded, randomized, placebo-controlled, gestational-age stratified superiority trial of those undergoing abortion or intrauterine fetal demise between 16 and 20-weeks gestation at Stanford Health Care and evaluate the following aims:

> **Aim 1** (Primary outcome). Determine if fewer pregnant people receiving cabergoline have breast symptoms post abortion/ post fetal expulsion compared to placebo. Participants will complete a survey to assess symptoms, using the validated Bristol Breast Symptoms Inventory at baseline and on days 2, 4, 7, and 14 post procedure. Based on physiology and prior symptom data, Day 4 will serve as our primary outcome.
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> **Aim 2** (Secondary outcomes). Determine if those receiving cabergoline report higher satisfaction, acceptability, and similar side-effects compared to placebo.

Background and significance

Lactogenesis

Stage I lactogenesis (secretory initiation) starts around 16 weeks gestation when high levels of estrogen, progesterone, and prolactin stimulate anatomic growth of breasts (1). High levels of estrogen and progesterone antagonize prolactin's synthesis of lactose. Stage II lactogenesis (secretory activation) starts after the removal of the placenta with a rapid drop in progesterone. The fall in progesterone removes the antagonizing effect on prolactin to start milk production, resulting in swelling of the breasts and milk production that starts 2-3 days postpartum. Breast engorgement occurs when lactation supply exceeds what is expressed from breasts. In the absence of physical stimulation, lactation eventually stops. Among those who do not breastfeed, milk leakage and breast pain begin between 1 to 3 days postpartum and engorgement begins between 1 and 4 days postpartum, all symptoms peaking 4 days postpartum and continuing up to three weeks (6).

Lactogenesis in second-trimester abortion or loss

Breast pain following second-trimester abortion is common. In a prospective, longitudinal study that followed pregnant people after a 14-20 week fetal loss, 50% reported breast tenderness, 45% engorgement, and 20% milk leakage on day 3 post-procedure (2).

Emotional distress

A prior qualitative study of pregnant people with a fetal demise occurring in the late second trimester found that they universally did not expect to lactate (7). Prior qualitative work surrounding mid-trimester perinatal loss suggests that breast engorgement and milk leakage causes physical pain and emotional distress (3).

Nonpharmacologic treatment of breast engorgement

Managing painful engorgement in those choosing not to breastfeed has been described by physicians and midwives for centuries. Midwifery techniques including belladonna ointment, intermittent expulsion, ice packs, and analgesics have been described but not rigorously studied for superiority. A Cochrane Review of

nonpharmacologic interventions for breast engorgement found that there was no evidence that any non-pharmacologic intervention resulted in a quicker resolution of symptoms (8).

Preliminary work

We conducted a double-blinded, block-randomized superiority trial comparing cabergoline 1 mg once to placebo for preventing bothersome breast engorgement after later second-trimester (18-28 weeks gestation) uterine evacuation (5). At baseline, report of breast symptoms was similar between people randomized to receive cabergoline and those randomized to placebo. On day 4, significantly fewer participants reported any breast symptoms (our primary outcome) in the cabergoline group compared to placebo (27.8% vs 97.0%, $p<0.001$) This difference was significant in all four domains of breast symptoms: engorgement (RR 0.17 [95% CI 0.07-0.45]), breast tenderness (RR 0.18 [95% CI 0.08-0.42]), leaking milk (RR 0.36 [95% CI 0.24-0.53]), and requiring pharmacologic pain relief (RR 0.39 [95% CI 0.26-0.59]). On day 4, 2.8% of those randomized to cabergoline reported significant bother from breast symptoms compared to 29.7% randomized to placebo ($p=0.001$). In an exploratory analysis of those less than 20-weeks gestation (cabergoline n=10, placebo n=9), 30.0% of those receiving cabergoline reported breast symptoms on day 4 compared to 100% of those that received placebo. While underpowered to make definitive claims on efficacy at this earlier gestational age, this provides us reassurance to proceed with the proposed study.

Project design and methods

Study Locations

Patients will be recruited at Stanford Gynecology Clinic in Palo Alto, CA and Planned Parenthood Mar Monte (PPMM) in San Jose, 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. Medicaid covers abortion care. Stanford University has an established relationship with PPMM, which includes providing regular abortion care services and collaborating on research. Our affiliation with this high volume, outpatient facility allows us to efficiently recruit study subjects, making this a feasible project. Many patients at PPMM receive abortion funds to pay for their abortions. The multi-site design will ensure a large catchment area of geographically and socioeconomically diverse patients to increase external validity.

Research Design and General Methodological Approach

The proposed study is similarly designed as a double-blinded, placebo-controlled, gestational-age stratified (16/0-17/6, 18/0-19/6 weeks gestation) superiority trial to evaluate cabergoline's role in relieving breast engorgement after second-trimester abortion or fetal demise. We will again capture breast symptoms using the validated Bristol Breast Inventory (9). A superiority design was selected as cabergoline is fairly expensive with possible side-effects. For this study to be practice-changing, cabergoline needs to demonstrate clear superiority over placebo.

The use of cabergoline for lactation inhibition after a third trimester delivery has been clearly established (4). Our own work has recently been presented and published, leading to inclusion of cabergoline into more clinical protocols more in the late second trimester (5). The aim of this study is to establish cabergoline's benefit in the early second trimester – a more common experience among pregnant people. As many free-standing, independent clinics only offer abortion care to 19 weeks 6 days gestation, we want to ensure that there is evidence for using cabergoline in our broader community.

We estimate that 15 subjects in each gestational-age strata (16/0-17/6 and 18/0-19/6 weeks gestation) are required to show a 45% decrease in those reporting breast symptoms compared to the control group, with a power of 0.8 and an alpha of 0.05. We plan to recruit 72 subjects, anticipating 10% missing data and loss to follow up.

Day #0 – Pre-operative visit/Cervical preparation visit

Eligible patients who are scheduled for an abortion or are diagnosed with an intrauterine fetal demise between 16-20 weeks gestation will be approached to enroll in the study. A research staff member will obtain informed consent and randomization will occur. Basic demographic information will be collected and entered into REDCap by a research coordinator (10). Standard demographics, gender identity, prior breastfeeding/ chestfeeding experience, and prior breast surgery will be asked of participants. A baseline Bristol Breast

Inventory questionnaire will be performed to establish existing breast symptoms related to pregnancy followed by a 7-point Likert bother scale. Patients will be randomized and drug distributed (cabergoline or identical placebo) to be taken after the procedure on day #1.

Day #1 – Procedure/ Induction Day
Dilation and evacuation (D&E) (procedural abortion) is performed in the outpatient gynecology clinic or ambulatory surgical center, depending on patient preference and other medical considerations. Those seeking induction abortion (medication abortion) will be admitted to Labor & Delivery until fetal expulsion occurs. All participants will receive standard information on support bras, analgesics, and cold compacts. Discharge instructions will instruct patients to take the study drug upon returning home after discharge to increase external validity outside of a trial setting. Patient will later be asked if they took the drug on day #1.

Days # 4-14 – Follow-up
Electronic, online surveys regarding breast symptoms using the Bristol Breast Inventory, and a 7-point Likert Scale to assess bother of symptoms and side effects will be collected on Days 2, 4, 7, and 14. Surveys will be sent via text message over RedCap at 08:00. A phone call will be made to participants between 17:00-20:00 if the survey is not completed that day.

An electronic gift card will be sent to the participant after 14 days. Participants will receive [redacted] per survey completed with a [redacted] bonus for completing all surveys on time for a maximum of [redacted] for full participation. With consent, the gift card will be distributed by e-mail or mobile phone number via Tango. Participants will have the opportunity to forego the gift certificate and donate funds to a reproductive health organization.

Criteria for Selection of Subjects

Inclusion: pregnant people, ages 18 years or older; intrauterine pregnancy between 16/0-19/6 weeks of gestational age (by ultrasound dating performed prior to or same day of enrollment visit); consented for an induced, elective abortion or undergoing management of demise; English or Spanish speaking, able to consent for a research study, literate in English or Spanish; willing to comply with study procedures and follow-up; access to a smart phone throughout the study.

Exclusion: prior mastectomy, currently breastfeeding, currently receiving dopamine agonist therapy for other indication (prolactinoma, Cushings syndrome, acromegaly, restless leg syndrome), contraindication to cabergoline (as per package insert), current use of dopamine antagonists (phenothiazines, butyrophenones, thioxanthenes, or metoclopramide)

Subject Recruitment and Allocation

Subjects will be recruited from Stanford Gynecology Clinic or Planned Parenthood Mar Monte on the day of their Family Planning consultation, after consent for but prior to abortion, or after diagnosis of intrauterine fetal demise. 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

Cabergoline is a long-acting dopamine receptor agonist with a high affinity for D2 receptors. It is FDA approved for the treatment of hyperprolactinemic disorders, either idiopathic or due to pituitary adenomas (FDA package insert). We will be using cabergoline off-label.

Data Management & Analysis

Stanford University has a license for the RedCap data management system (10). REDCap is a web-based application that is secure, reliable, and HIPAA-compliant for storing research study data. REDCap is designed with built-in features to address confidentiality and compliance requirements. Electronic, online surveys will be sent via text message over RedCap on Days 2, 4, 7, 14. 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. SAS OnDemand will be used for data analysis. Data will be analyzed with parametric or non-parametric statistical tests, as

appropriate. Stratified analysis and logistic regression will be performed to assess demographic characteristics as predictors of breast symptoms and associated distress.

Summary

Breast engorgement after second-trimester abortion or fetal loss is highly bothersome but has not previously been identified as a target of intervention by the medical community because, while physically and emotionally uncomfortable, is not otherwise dangerous and has been the prevalence and bother have been underestimated by clinicians. This trial represents an opportunity to improve patient experience during an otherwise challenging, often stigmatized, reproductive event.