Cabergoline for Lactation Inhibition After Second-Trimester Abortion or Loss (LISTA)

Study Protocol and Statistical Analysis Plan

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1. Brief Summary

Breast pain following second-trimester abortion is common. (Hagey 2020, Andersen 1990) Breast engorgement and milk leakage following second-trimester perinatal loss and abortion can cause both physical pain and emotional distress. (Seresheti 2016) Dopamine agonists have previously been shown to be effective in lactation inhibition for third-trimester fetal/neonatal loss or contraindications to breastfeeding. (Tulloch 2019) In a head-to-head trial, cabergoline was more effective with a better safety profile than bromocriptine and has thus emerged as preferred treatment for term lactation inhibition internationally. (Harris 2020, Giorda 1991, European 1991) Despite the frequency of breast symptoms after second-trimester abortions, there are no current guidelines for this population.

We will conduct a double-blinded, placebo-controlled, superiority trial of those undergoing abortion or intrauterine fetal demise between 18 and 28-weeks gestation at Stanford Health Care. Participants will be randomized to either cabergoline 1mg 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, 3, 4, 7, and 14 after the procedure. (Bristol 1966) Our primary outcome is breast symptoms on Day 4. Secondary outcomes include satisfaction, acceptability, and side-effects. We hypothesize that cabergoline is superior to placebo for preventing breast engorgement after second-trimester abortion or loss. We estimate that 32 subjects in each group are required to show a 30% 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 100 subjects, anticipating 30% missing data and loss to follow up. Electronic, online surveys regarding breast symptoms and side-effects will be sent via text message. (Friedlander, 2020) A sub-study of 10 participants will return for serum prolactin levels on Days 2, 4, 7, 14.

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

2. Background

2A. Lactogenesis

Lactogenesis is a two-stage physiologic process of developing the ability to secrete milk that starts from 16th week of pregnancy and continues after delivery regardless of the birth outcome (Lawrence 2011). Stage I lactogenesis (secretory initiation) takes place during the second half of pregnancy where high level of estrogen, progesterone, and prolactin stimulate anatomic growth of breasts. Prolactin initiates lactose synthesis in alveolar cells which remains inhibited by high levels of estrogen and progesterone secreted by the placenta during this stage in pregnancy.

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 postpartum days 2-3. Breast engorgement happens when lactation supply exceeds what is expressed from breasts.

Prolactin is a peptide synthesized in the anterior pituitary and is both positively and negatively regulated. Regular expression of milk and nipple stimulation triggers prolactin release. Dopamine released by the hypothalamus acts as an inhibitory factor to prolactin release by stimulating D2 receptors in the anterior pituitary. The normal range in non-pregnant, non-lactating assigned female at birth is 5-23 μg/L.

In 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 3-5 days postpartum and continuing up to three weeks. (Spitz, 1998, Melis 1988).

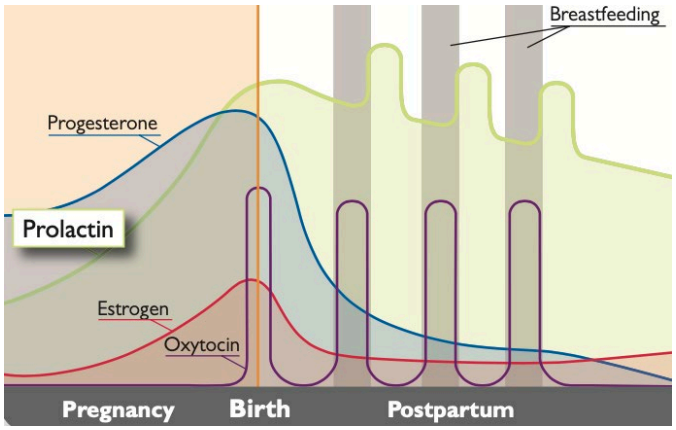


Figure 1. Stage I lactogenesis (secretory initiation) takes place during the second half of pregnancy where high level of estrogen, progesterone, and prolactin stimulate anatomic growth of breasts. Stage II lactogenesis (secretory activation) starts after the removal of the placenta with a rapid drop in progesterone. The fall in progesterone removes the antagonizing effect on prolactin. (Love 1990)

2B. Lactogenesis in second-trimester abortion or loss

Breast pain following second-trimester abortion is common. In a prospective, longitudinal study following women after a 14-20 week fetal loss of abortion found on day 3 post-procedure, 50% reported breast tenderness, 45% engorgement, and 20% milk leakage (Hagey 2020).

We can further characterize baseline incidence of breast symptoms after second-trimester abortion from the placebo and no treatment arms of published randomized clinical trials of pharmacologic methods for lactation suppression. In a three-arm study testing bromocriptine after second-trimester loss or abortion occurring 15-26 weeks gestation, participants were randomized to bromocriptine vs placebo vs no treatment. (Andersen 1990) Utilizing subjective recordings of breast pain and milk secretion, they found the peak breast pain and milk secretion occurred on days 3-7 post-procedure, with only 9% of patients were completely free of breast symptoms in the placebo and no treatment groups.

2C. Emotional distress

In a prior qualitative study of those with a neonatal demise occurring between 19-27 weeks gestation found that they universally did not expect to lactate. (Chen 2015) Prior qualitative work surrounding mid-trimester perinatal loss suggests that breast engorgement and milk leakage causes physical pain and emotional distress. In interviews with 18 individuals with a second trimester perinatal loss or abortion, all reported pain and sensitivity of the breasts between 2nd and 5th day after perinatal loss (Sereshti 2016). Four themes were extracted from the interviews: (1) breast engorgement and leaking was seen as reminder of the loss, (2) it was challenging to reconcile the motherhood identify associated with lactation with the absence of an infant, (3) frustration surrounding lack of knowledge about milk leakage and available remedies, and (4) pain and disability from lactation exacerbating psychological pain from the loss.

2D. Special populations

Not all individuals that become pregnant identify as women. In contrast to a mastectomy, chest masculinization "top" surgery removes most but not all mammary tissue (Garcia-Acosta 2019). Prior qualitative studies on the experience of pregnancy for transgender men reports a significant amount of gender dysphoria associated with chestfeeding. (MacDonald 2016) Participants described situations where growth of chest tissue affected how their gender was perceived by others. Having prominent chest tissue resulted in individuals being identified by others as female more often than other typically female secondary sex characteristics, including a gravid abdomen. Some participants with a history of prior chest masculinization surgery experienced engorgement and early signs of mastitis. As unintended pregnancy leading to termination may be further stigmatizing for transgender men and the

risk of unintended pregnancy in this population is high, they may particularly benefit from lactation inhibition and we plan to include them in our study. (Charlton 2020)

2E. 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 (Spitz 1998). In a randomized control trial of binder or support bra for lactation inhibition after term delivery, breast-binder group reported a greater degree of breast tenderness and breast leakage but there was no difference in breast engorgement on day 4. (Swift 2003) However, both groups experienced a high rate of rebound lactation within 14 days. A Cochrane Review of nonpharmacologic interventions for breast engorgement found that there was no evidence that ultrasound, cabbage leaves, or oxytocin were associated with a more rapid resolution of symptoms. (Mangesi 2010) The use of cold packs was not found to cause harm but may not be associated with improvements in symptoms. While standard of care at this time in the United States is to offer cold compresses and support bras, these are non-evidence-based interventions, further emphasizing the need for effective intervention in this population.

2F. Dopamine agonists for lactation inhibition
There is both biologic plausibility and existing evidence that a dopamine agonist can antagonize prolactin release which then leads to cessation of lactogenesis.

Early research showed bromocriptine 2.5mg twice daily for two weeks after second-trimester abortion caused a significant reduction in breast tenderness, milk secretion, and serum prolactin levels on day 4 compared to placebo. (Andersen 1990) Prolactin levels were suppressed more effectively with bromocriptine with 89% achieving serum prolactin levels less than 23 micrograms/L on day 4 as compared to only 28% with placebo.

Bromocriptine (0.25mg twice daily for 14 days) was then compared to cabergoline (1mg once, day of procedure) in a large, multi-center randomized control trial after term delivery. (European 1991) On postpartum day 3, a complete absence of breast symptoms was reported in 90.4% of individuals in the cabergoline group and 83.8% in the bromocriptine group. Cabergoline continued to be superior for the entire observation period of 21 days where an absence of symptoms was significantly better with cabergoline (74%) than with bromocriptine (51%). In a sub-study where serum prolactin levels were measured up to 21 days after delivery, the initial drop in mean prolactin levels was more dramatic from delivery to day 2 for cabergoline (131.3 µg/L to 26.3 µg/L) compared to bromocriptine (129.9 µg/L to 45.5 µg/L). Bromocriptine also showed a considerable prolactin rebound after day 15 which was not observed in the cabergoline group.

In a dose-finding study comparing a single dose of cabergoline 1mg, 0.75mg, 0.5mg or placebo after term delivery resulted in complete absence of breast symptoms in 90%, 70%, 45%, 20%, respectively of participants up to day 14 postpartum. (Caballero 1991) Similarly, a dose-finding study of a single dose of cabergoline 0.8mg, 0.6mg, 0.4mg or placebo after term delivery reported no milk secretion in 100%, 100%, 50%, 12.5%, respectively (Mellis 1998). Prolactin levels dropped significantly for the three experimental doses compared to the placebo group on days 1-3 postpartum.

2G. Current uses of cabergoline for lactation inhibition
Pharmacologic lactation inhibition has previously been studied in individuals with HIV to avoid vertical transmission. A scoping review of postpartum pharmaceutical lactation inhibition specific for individuals with HIV summarized five studies that focused on this issue, all of which found cabergoline effective and safe in this setting. (Tulloch 2019)

While the World Health Organization's 2016 "Updates on HIV and infant feeding" does not include guidelines on lactation inhibition, multiple country-specific guidelines recommend measures to manage symptomatic breast

engorgement for those for whom breastfeeding is contraindicated. In 2008, the British "Guidelines for the management of HIV infection in pregnant women" first suggested for the use of cabergoline. Their 2018 guidelines strengthened the recommendation where cabergoline should be offered cabergoline to suppress lactation.

The 2020 United States Department of Health and Human Services Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission now recommends the use of cabergoline to suppress breast milk production after a shared decision-making discussion regarding limited data about its use, potential side-effects, and the limited availability of non-pharmacologic alternatives.

2H. Safety

In a recent, large systematic review including 25 articles for a total of 757 participants investigating cabergoline for postpartum lactation inhibition, adverse events were observed in 14.2%. (Harris 2020) Symptoms were generally mild, transient, and self-resolving. The most common events were dizziness (4.6%), headache (3.9%), and nausea or vomiting (2.5%), typical of the dopaminergic class. Only 5 of the 757 participants required medication for adverse symptoms. Less common events were abdominal or epigastric pain, breast pain or tension, vertigo, palpitations, epistaxis, and drowsiness. No serious adverse events were reported. There is a theoretical risk of dopamine agonists potentiating psychiatric illness; this review identified four case reports where cabergoline was initiated following a diagnosis of postpartum psychosis without exacerbation of psychiatric outcomes. In another two cases, cabergoline was initiated for lactation inhibition with reports of psychotic symptoms developing within two days of treatment; in both of these cases, symptoms were well-controlled with initiation of antipsychotic medications and remains unclear if cabergoline was provoking.

The safety of bromocriptine for lactation inhibition was called into question in 1984, when the US Food & Drug Administration (FDA) called attention to reports of postpartum hypertension, seizures, and strokes associated with the use of bromocriptine. (Rayburn 1996). While no studies found an increased incidence of these events compared to placebo or anticipated postpartum incidence, the FDA ultimately asked the manufacturer in 1990 to voluntarily stop selling bromocriptine as a lactation suppressant.

In addition to the existing data showing safety of cabergoline, there is theoretic biologic plausibility as to why cabergoline is better tolerated than bromocriptine. Cabergoline has a greater affinity for D2 receptors, longer plasma half-life, and flat plasma drug concentration resulting in a shorter required duration of therapy compared to bromocriptine. (Rains 1995) Notably, in Canada, the UK, and France, cabergoline has an approved indication for the prevention of physiologic postpartum lactation.

3. Research Questions

We are aiming to answer whether cabergoline is superior to placebo at preventing breast symptoms after second-trimester abortion or loss. The goal is to improve patient experience and establish a standard of care for lactation inhibition after second-trimester abortion or loss.

Our primary outcome is breast symptoms on Day 4 post-abortion/ post fetal expulsion. Secondary outcomes include initiation of milk secretion, satisfaction, acceptability, and side-effects.

We will test the following hypotheses:

1. A smaller proportion of those receiving cabergoline will report breast symptoms on Day 4 compared to placebo.
2. Prolactin levels will be significantly lower on Day 4 in those receiving cabergoline compared to placebo.
3. The proportion of participants ever reporting secretion of milk within 14 days post-procedure will be lower in those receiving cabergoline compared to placebo.
4. Participants receiving cabergoline will be more satisfied with their post-procedure breast symptoms compared to those receiving placebo.

5. Side-effects will occur in less than 10% of patient and not differ between those receiving cabergoline compared to placebo.

4. Methods

4A. Research Design and General Methodological Approach

The study is designed as a prospective double-blinded, placebo-controlled, superiority trial to evaluate cabergoline's role in relieving breast engorgement after second-trimester abortion or fetal demise. Breast symptoms will be defined by the validated Bristol Breast Inventory score. (Bristol 1966)

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.

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 18–28 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. (Harris 2009) 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.

Standard counseling regarding medical or surgical management will be provided, as applicable. A complete history and physical will be performed. If an ultrasound report is not available to confirm gestational age dating, an informal, bedside abdominal ultrasound will be performed to determine gestational age. All patients will receive mifepristone 200mg PO. Those choosing D&E will also have osmotic dilators placed. Participants over 22 weeks with a viable intrauterine pregnancy will receive feticidal injection with either lidocaine or digoxin as is standard practice at these sites. Standard of care antibiotics for prophylaxis will be provided, if indicated.

Day #1 – Procedure/ Induction day

Dilation and evacuation (D&E) are done in the outpatient gynecology clinic or ambulatory surgical center, depending on patient preference and other medical considerations. All participants will receive pre-procedure misoprostol 90 minutes prior to procedure as is standard practice at our site.

Those seeking medical abortion or those with fetal demise over 24 weeks gestation will be admitted to Labor & Delivery where they will receive repeat doses of misoprostol 400 mcg buccal every three hours until fetal expulsion occurs.

Those in the serum sub-study will have a prolactin level drawn at the time of intravenous (IV) insertion. Rhogam will be provided if indicated.

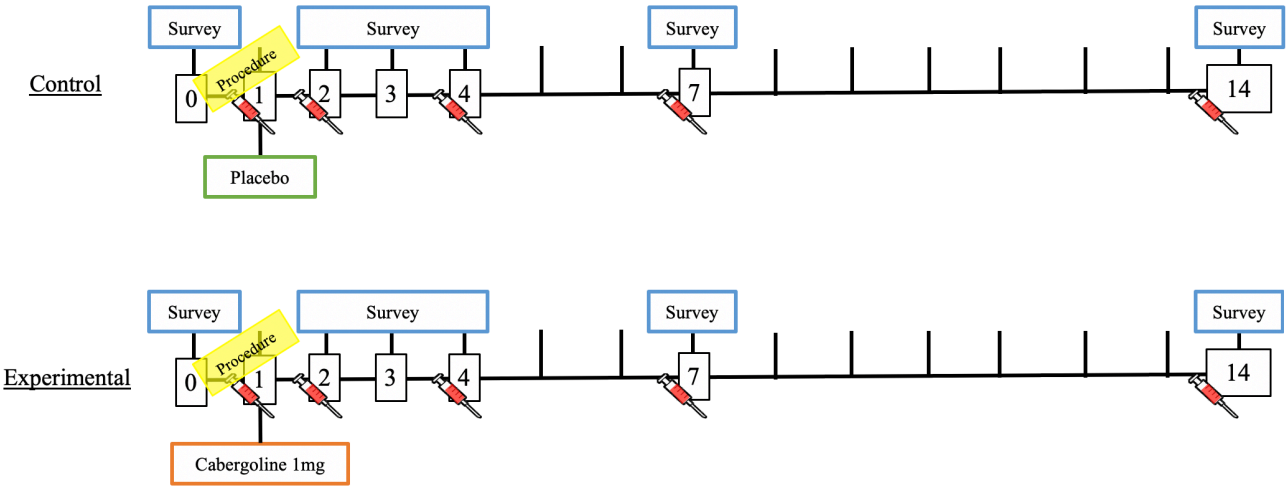
Within 4 hours of fetal expulsion and prior to discharge, the study coordinator will distribute the study drug or placebo as randomized on Day #0. All participants will receive standard information on support bras, analgesics, and cold compacts.

Days # 2-14 – Follow-up

Electronic, online surveys regarding breast symptoms using the Bristol Breast Inventory, 7 point Likert Scale to assess bother of symptoms, current bleeding profile (Janssen 1995) and side-effects will be collected on Days 2, 3, 4, 7, 14. Additionally, participants will be asked on Day 14 to rate overall acceptability of the protocol, likelihood to recommend to a friend, and willingness to pay. Surveys will be sent via text message over RedCap at 08:00. (Friedlander 2020) A phone call will be made to participants between 17:00-20:00 if the survey is not completed that day. Day 14 survey will include measures of willingness to pay and overall satisfaction.

A substudy of 10 patients enrolled at Stanford (5 cabergoline, 5 placebo) will return to Stanford laboratories for repeat serum prolactin levels on Day 2, 4, 7, 14.

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 five surveys on-time for a maximum of $[redacted] for full participation. Those participating in the serum prolactin sub-study will receive $[redacted] per phlebotomy session with a bonus $[redacted] for completing all lab draws on the appropriate day for a maximum of $[redacted] for full participation. With consent, the gift card will be distributed by e-mail or mobile phone number via Amazon. For patients who prefer a physical gift card, it will be mailed to their reported address. Participants will have the opportunity to forego gift certificate and donate funds to a reproductive health organization.



4B. Criteria for selection of subjects

Inclusion:

Pregnant people, ages 18 years or older
Intrauterine pregnancy between 18/0-28/0 weeks of gestation age (by ultrasound dating performed prior to or same day of enrollment visit)
Consented for an induced, elective abortion or undergoing induction for 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 smart phone throughout study

Exclusion:

Prior mastectomy (breast reduction or chest masculinization surgery acceptable)
Currently breastfeeding
Currently receiving dopamine agonist therapy for other indication (prolactinoma, Cushings syndrome, acromegaly, restless leg syndrome)
Contraindication to cabergoline (as per package insert)

- Uncontrolled hypertension – defined as baseline BP > 150/100, or chronic hypertension requiring more than one baseline medication, or pregnancy-induced hypertension spectrum disorders (gestational hypertension, preeclamspia, eclampsia)
- History of cardiac valvular disorders or valvular repair
- History of pulmonary, pericardial, or retroperitoneal fibrotic disorders

- Current use of D2 antagonists (phenothiazines, butyrophenones, thioxanthenes, or metoclopramide)

4C. 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 or the Lucille Packard Childrens Hospital Labor & Delivery 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.

4D. 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.

4E. Laboratory and Other Investigations
A substudy of 10 participants (5 cabergoline, 5 placebo) will return to Stanford laboratories for repeat serum prolactin levels on Day 2, 4, 7, 14. The Stanford laboratory runs serum prolactin on a electrochemiluminescence immunoassay with a working range of was 0.5–150 μg/L and interassay coefficient of variation is 4.68%. The reference range in this lab for non-pregnant, non-lactating female-assigned at birth is 4.8−23.3 μg/L.

4F. Data Management & Analysis
Stanford University has a license for the RedCap data management system. (Harris 2009) 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, 3, 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 associate distress.

A Data and Safety Monitoring Committee (DSMC) will be used given that the use of cabergoline for lactation inhibition is a new and unfamiliar intervention and limited data exists for this use. A DSMC will be formed to monitor the progress of the study and review any of the following events under the Data and Safety Monitoring Plan: (i) Adverse events and/or serious adverse events will be recorded in our data collection tool, REDCap (ii) The research coordinator will be responsible for directly monitoring the data and compliance with the protocol. All events will be immediately reported to the principal investigator/sponsor. The sponsor will be responsible for reporting any adverse or serious adverse events to the DSMC members and IRB (iii) Serious adverse events and unanticipated problems will be reported immediately to the monitoring committee and any events of stroke, hospitalization for hypertensive emergency, hospitalization for psychiatric condition will lead to immediate termination of the study (iv) Side-effects that are common according to the FDA package insert including nausea/vomiting, headache, dizziness, orthostatic hypotension, constipation, abdominal pain, fatigue will be reported to the DSMC during a planned interim analysis and the committee will review the progress of the study and assess these safety events after 50% planned recruitment achieved (v) Outcome of the interim analysis from the DSMC will be communicated to the IRB by the principal investigator. All adverse events will be summarized with special attention to events that may be related to the study drug.

5. Study Population
Number of Subjects and Statistical Power
Incidence of symptomatic breast engorgement after second-trimester abortion has been reported to occur between 50-91% of individuals (Hagey 2020, Anderson 1990). In prior studies of term lactation inhibition using

cabergoline 1 mg, complete absence of lactation was noted in 78-100% of study subjects (European 1991, Mellis 1998, Giorda 1991, Caballero 1991). We estimate that 41 subjects in each group are required to show a 30% decrease in those reporting breast symptoms compared to the control group, with a power of 0.8 and an alpha of 0.025 (planned interim analysis). We plan to recruit 100 subjects, anticipating 10% missing data and loss to follow up.

Based on the prior RCT comparing bromocriptine to placebo after second-trimester abortion, the mean serum prolactin level in the placebo group was 44±8 μg/L on Day 4 and 12.2+2 μg/L in the bromocriptine group (Andersen 1990). The upper-limit of normal for a non-lactating female-assigned at birth is 23 μg/L. We will need 8 patients to have a 90% chance of detecting, at the 5% significance level, a decrease in serum prolactin from 44 in the control group to 23 in the experimental cabergoline group. We will recruit 10 subjects, anticipating 20% loss to follow up and missing data.

Locations
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 practices and Planned Parenthood Mar Monte California. Medicaid covers abortion care through 23/6 weeks. In 2019, we performed 72 abortions between 18/0 and 23/6 weeks gestation at Stanford University and the Lucille Packard Childrens Hospital admitted an average of 1 patient each month for medical abortion or fetal demise between 18-28 weeks gestation.

6. Timeline
With an anticipated 66% enrollment, we anticipate enrollment to take 19 months.

Year 1	Sept-20	Oct-20	Nov-20	Dec-20	Jan-21	Feb-21	Mar-21	April-21	May-21	June-21	
Consent development	x	x									
Survey development	x	x									
IRB review		x	x	x							
Recruitment					x	x	x	x	x	x	
Data collection					x	x	x	x	x	x	
Year 2	July-21	Aug-21	Sept-21	Oct-21	Nov-21	Dec-21	Jan-21	Feb-21	Mar-21	April-21	May-21
Recruitment	x	x	x	x	x	x	x	x	x		
Data collection	x	x	x	x	x	x	x	x	x		
Interim analysis	x										
Data analysis		x							x	x	
Manuscript										x	x

7. Use of Research Results
We aim to present the findings at the ACOG Annual Clinical Meeting in spring 2022 as we believe these data will be broadly applicable for MFMs and generalist obstetricians caring for second-trimester losses in additional to Complex Family Planning subspecialists. We also plan to publish the findings in a peer-reviewed journal and work with the Society of Family Planning and ACOG on guideline development. Results will also be used to inform future studies including a cost-effectiveness analysis.