TITLE Efficacy of Cabergoline in Inhibiting Lactation and Alleviating Breast Symptoms After 12-18 Week Abortion or Pregnancy Loss: A Pilot and Randomized Controlled Trial

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FUNDING SUPPORT
Maimonides Research and Development Foundation

APPROVAL DATE
February 27, 2026

APPROVAL NUMBER
2025-07-24

NCT
NCT ID not yet assigned

INTRODUCTION

BACKGROUND AND SIGNIFICANCE

Second-trimester spontaneous and induced abortions are often accompanied by significant physical discomfort. While patients and providers usually focus on pelvic pain, breast symptoms are actually very common, as lactogenesis begins as early as 12-20 weeks of gestation. For example, Hagey et al found that 50% of patients undergoing abortion or pregnancy loss between 14 and 20 weeks experience breast tenderness, while 45% report breast engorgement, and 20% report lactation.[2] However, the frequency of breast symptoms in the early second trimester has not been adequately assessed.

Due to the bothersome and potentially upsetting nature of these symptoms, several studies have aimed to identify a pharmacologic solution to stop pregnant people from experiencing them. A randomized controlled trial in 1990 identified that bromocriptine was effective at inhibiting lactation and breast symptoms for induced or spontaneous abortions between 15 and 26 weeks.[3] However, bromocriptine was also found to be associated with significant cardiovascular, neurologic, and psychiatric side effects, and, in two patients, death.[4] In fact, bromocriptine was pulled from the US market for lactation suppression due to these concerns.[5] Cabergoline then emerged as a possible safer lactation suppression medication. The drug is a newer ergot derivative, part of the same drug class as bromocriptine, that lowers the activity of prolactin, a hormone that is needed for lactation.[6] Two subsequent systematic reviews identified cabergoline as not only safe to use for lactation suppression, but also associated with less dizziness, headache, and nausea compared to bromocriptine.[7,8] Subsequently, two trials and a review found that cabergoline is as effective as bromocriptine in suppressing lactation symptoms.[6,9] However, these studies assessed lactation suppression after full-term deliveries.

Recently, two randomized controlled trial by Henkel et al found that cabergoline is effective in reducing breast symptoms in those undergoing spontaneous and induced abortion between 14 and 28 weeks.[10,11] Among 69 participants, significantly fewer participants receiving cabergoline reported any breast symptoms compared with placebo including engorgement, milk leakage, tenderness, and the need for pain relief (27.8% vs 97.0%, P<.001), and fewer reported significant bother (2.8% vs 33.3%, P=.001) 4 days after their abortion. Subsequently, a prospective cohort study identified cabergoline as acceptable and associated with an improvement in breast symptoms from 14 to 24 weeks gestation.[12]

Despite the success of these studies, the treatment of these breast symptoms earlier than 14 weeks has not been adequately evaluated in the literature. This study aims to (1) determine the frequency of breast symptoms in those undergoing abortion or pregnancy loss between 12-18

weeks, and (2) assess the efficacy of cabergoline for inhibiting lactation and breast symptoms in these patients. For many patients undergoing abortion or pregnancy loss in the early second trimester, their interactions with healthcare providers are often distressing. With this study, we hope to improve the patient experience with evidence-based methods to ameliorate discomfort.

STUDY OBJECTIVES

1. To assess the frequency of breast symptoms including engorgement, milk leakage, tenderness, and need for pain relief among pregnant people with 12-18 week pregnancies undergoing treatment for spontaneous or induced abortions at Maimonides Medical Center
2. To evaluate if cabergoline, given prophylactically post-abortion, decreases the frequency or severity of these breast symptoms

HYPOTHESIS

Patients undergoing treatment of a spontaneous or induced abortion at 12-18 weeks will experience frequent breast symptoms including engorgement, milk leakage, tenderness, and need for pain relief. Cabergoline will be effective in inhibiting lactation and decreasing the frequency of these symptoms.

STUDY DESIGN

Subjects: Patients undergoing termination of pregnancy or pregnancy loss between 12 and 18 weeks of gestation at Maimonides Medical Center

Eligibility Criteria:
Inclusion Criteria:
Pregnant people aged 18 years or older who are between 12 and 18 weeks of gestation undergoing abortion or pregnancy loss at Maimonides Medical Center.

Exclusion Criteria:
Patients with prior mastectomy, those currently breastfeeding, those currently receiving a dopamine agonist or antagonist for other indication, or those with a contraindication to cabergoline per the package insert, which includes:

- Uncontrolled hypertension or known hypersensitivity to ergot derivatives
- History of cardiac valvular disorders, as suggested by anatomical evidence of valvulopathy
- history of pulmonary, pericardial, or retroperitoneal fibrotic disorders

Design:

Our study will include two phases. In the first phase, we will survey pregnant people who have abortions between 12-18 weeks to determine the prevalence of breast symptoms. Through these surveys, we will understand how common breast engorgement, milk leakage, tenderness, and need for pain relief are experienced among this group. We will use the Bristol Breast Symptoms Inventory (see Attachment 1), a validated postpartum measure, to have patients rate the severity of their symptoms. The scale ranks each of the four domains of breast pain (breast engorgement, milk leakage, tenderness, and need for pain relief) on a scale of 1-4, where a lower score indicates less or no symptoms, and a higher score indicates more severe symptoms. This survey will be administered to all patients who meet eligibility criteria and complete informed consent prior to randomization for Phase 2. Based on our sample size calculation (see below), we estimate 348 participants will complete this initial survey. Given that Phase 1 and 2 will occur simultaneously and that the Phase 1 survey will occur immediately prior to randomization for Phase 2, all participants who enroll in Phase 2 will automatically complete Phase 1.

The second phase of this study will include a double-blinded randomized controlled trial, during which pregnant people who have spontaneous or induced abortions between 12 and 18 weeks will be randomized to oral cabergoline or placebo 1 hour after abortion. Both participants and providers will be blinded to randomization.

All patients who agree to participate will receive a single dose of either 1mg of cabergoline or a placebo directly following their abortion. They will then be asked to complete multiple surveys. The first survey will be a pre-intervention survey to assess baseline breast symptoms and will be done prior to pregnancy termination and completed in-person via REDCap. Subsequent surveys will be administered online on days 2, 3, 4, 7, and 14 following the abortion via REDCap. REDCap is a web-based password-protected application on a secure platform behind the Maimonides Medical Center firewall.

Invitations will be sent through email before 9 AM on the appropriate day. A phone call will be made to participants between 5:00 pm and 8:00 pm if the survey is not completed that day. If participants do not complete the survey on the day requested, their data will not be collected for that day. A subsequent email for the following survey will be sent as described above. Following completion of the Day 14 survey, a virtual gift card for 31 USD will be sent via Giftogram. A subgroup of participants, approximately 20, will be asked to return on days 0, 4, 7, and 14 to test serum prolactin levels. These participants will be chosen at random to offer a blood draw. Blood draws will not be mandatory to participate in either Phase 1 or 2 of the study. A single tube of blood will be drawn, averaging between 6-10mL, one time.

Data Collection Procedures:

Quantitative data will be collected during all parts of the study. Surveys will assess breast symptoms such as engorgement, milk leakage, tenderness, and need for pain relief. We will also measure serum prolactin levels.

Data Analysis:

Baseline characteristics between the two groups will be compared using X^2 and t tests. Descriptive statistics will be calculated to assess the baseline rate of breast symptoms in this population. For our primary outcome (percentage of patients with breast symptoms 4 days after procedure), we will use X^2 or Fisher exact testing, as appropriate. Using similar statistical testing, we will also compare the two groups on the four domains of breast pain (engorgement, milk leakage, tenderness, and need for pain relief). Secondary outcome measures of bother and satisfaction are ordinal in nature and their distribution is nonparametric; thus, we will compare the medians between groups with Wilcoxon rank sum test. Serum prolactin levels will be assumed nonparametric and compared with Wilcoxon rank sum test.

Sample Size:

We anticipate about 25% of participants will experience breast symptoms following their abortion, given that lactogenesis is thought to start at 12 weeks and the reported frequency of breast symptoms in the second trimester in the published literature. If our preliminary results indicate that less than 25% of participants experience breast symptoms, we will still continue with Phase 2 of the study, but acknowledge this as a limitation in our statistical analysis, as there still may be benefit to giving cabergoline at this gestational age range even if symptoms are less frequent. If this occurs, sub-analysis will be conducted to assess improvement in breast symptoms among those who were initially symptomatic.

Given that much of the literature suggests that cabergoline inhibits lactation and breast symptoms, we anticipate that cabergoline will have similar effects on our target population. Given a 95% confidence interval and a $p<0.05$, we will need to recruit 145 individuals per arm to see a 30% decrease in symptoms. To account for the possibility of a 20% loss to follow up we will recruit 174 individuals per arm. We aim to recruit 348 participants in total.

Expected Outcomes:

We expect that pregnant people with abortions during 2-18 weeks of gestation will experience breast symptoms including engorgement, milk leakage, tenderness, and need for pain relief. We expect that cabergoline will effectively reduce the frequency of these symptoms.

Timetable:

June 2025: Anticipated MRDF funding approval, IRB submission
November 2025 – November 2027: Data collection
March 2026 – December 2027: Data analysis
November 2027 – January 2028: Manuscript preparation and submission, presentation at national conferences

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