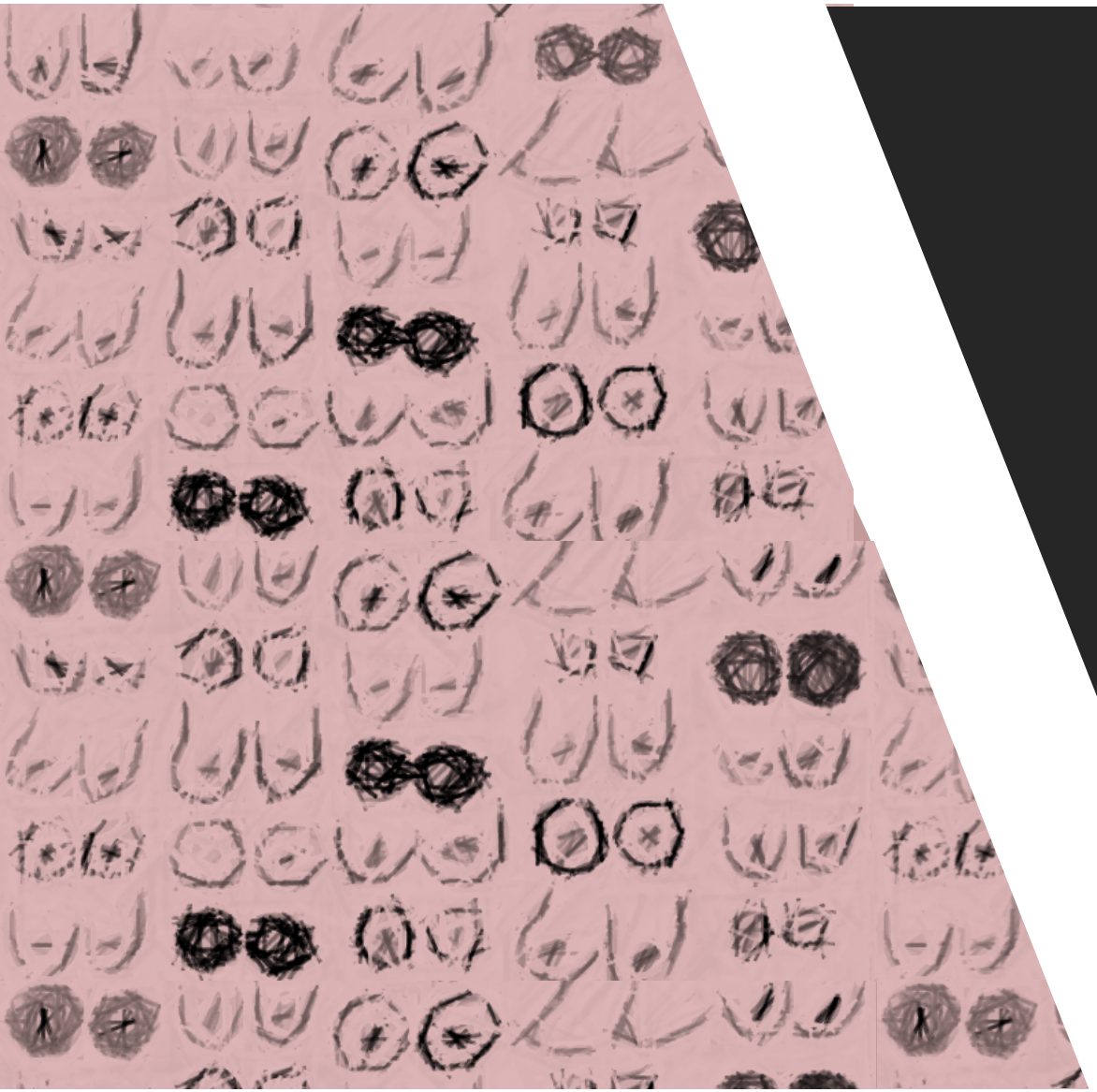

Cabergoline for Lactation Inhibition after Second-Trimester Abortion or Loss:

a planned interim analysis of a randomized controlled trial

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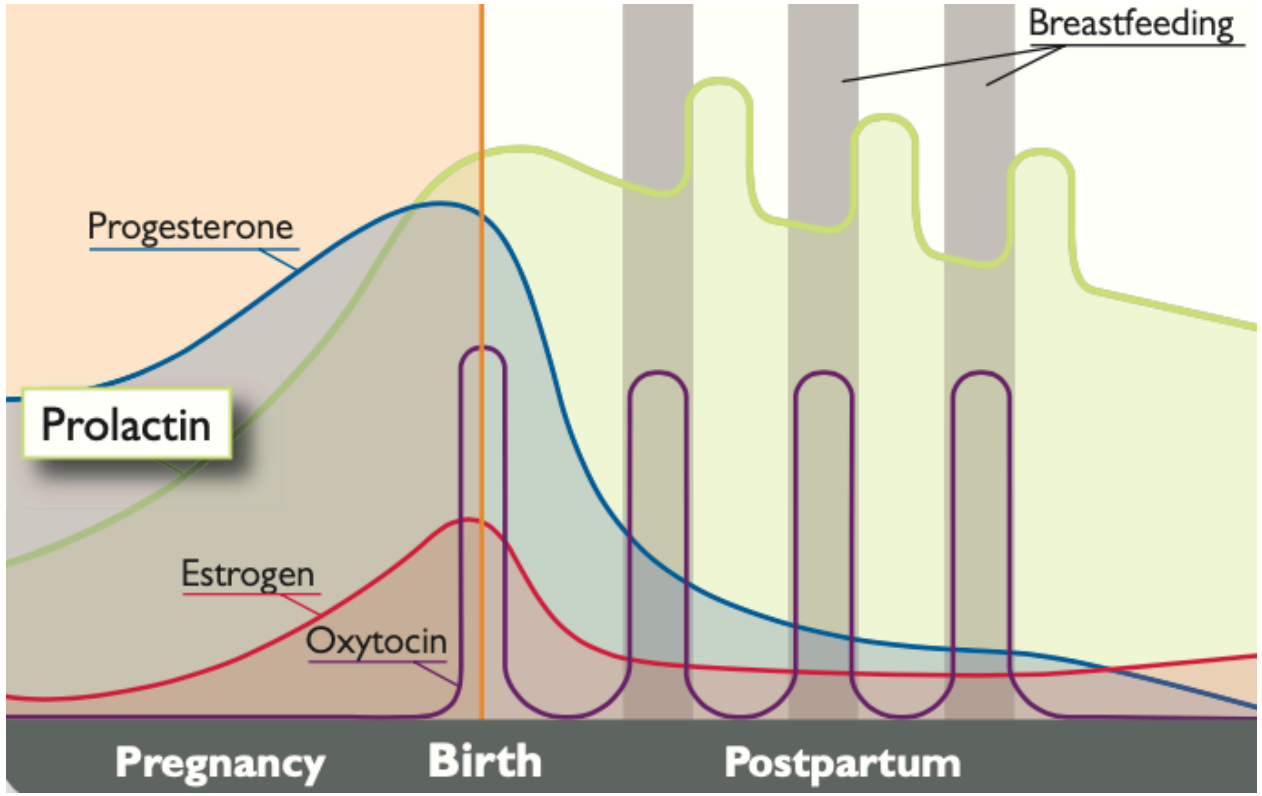
Disclosures

- No conflicts of interest

Background

- Stage I lactogenesis (secretory initiation)
  - Starts ~16 weeks gestation
  - 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
  - Fall in progesterone removes the antagonizing effect on prolactin
  - Peak engorgement postpartum day 4

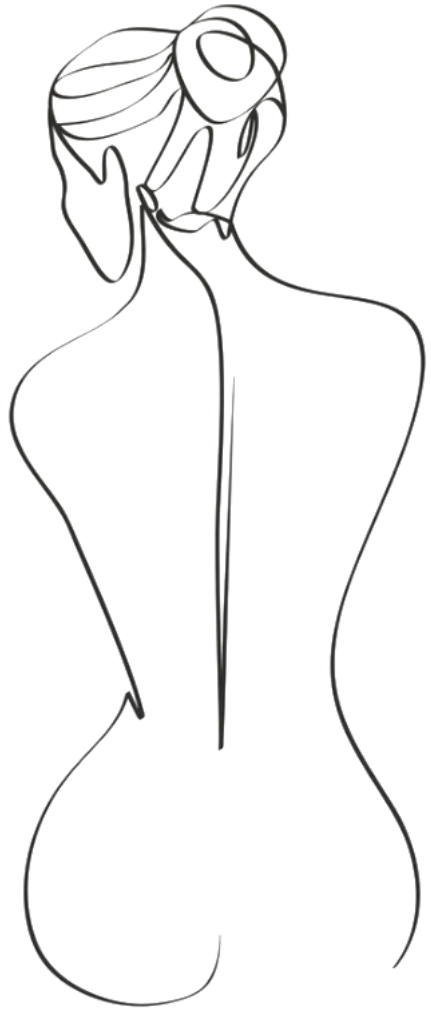


Lawrence RA, Lawrence RM. Breastfeeding: A guide for the medical profession. Maryland Heights, Missouri: Elsevier; 2011.

Background

- Breast engorgement and leaking was seen as **reminder of the loss**
- It was challenging to reconcile the **motherhood identity** associated with lactation with the absence of an infant
- **Frustration** surrounding lack of knowledge about milk leakage and available remedies
- Pain and disability from lactation **exacerbating psychological pain** from the loss

> It was not only the physical pain that bothered me, feeling pain in my breasts and knowing that there was milk and having no child to feed was agonizing.



Cole M. Lactation after Perinatal, Neonatal, or Infant Loss. Clinical Lactation 2012
Sereshti M et al. An exploration of the maternal experiences of breast engorgement and milk leakage after perinatal loss. Glob J Health Sci. 2016.

Background

Non-pharmacologic approaches:

- Breast binding
- Cabbage leaves
- Anti-inflammatory supplements
- Application of jasmine flowers
- Herbal remedies: sage, parsley, and peppermint
- High-dose vitamin B6
- Acupuncture

- Cochrane review: **no strong evidence that interventions lead to a more rapid resolution of symptoms** >> improvements in pain and symptoms over time regardless of treatment

Cole M. Lactation after Perinatal, Neonatal, or Infant Loss. Clinical Lactation 2012
Mangesi L et al. Treatments for breast engorgement during lactation. Cochrane Database Syst Rev. 2010

Methods

Does cabergoline prevent symptomatic breast engorgement after second-trimester abortion?

- **Trial design:** superiority, parallel group, double-blinded, block randomized (alternating 8 and 4), modified ITT
- **Inclusion:** pregnant people ≥18y, English- or Spanish-speaking, 18-28 weeks gestation seeking abortion care or management of fetal demise, internet access
- **Exclusion**: prior mastectomy, current dopamine agonist therapy for other indication, current dopamine antagonist use, contraindication to cabergoline

- Stanford IRB-approved: 5136 // Registered on clinicaltrials.gov: NCT04701333
- Funded by Society of Family Planning

- **Primary outcome:** presence of breast symptoms on Day 4
  - 33 particpants 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 0.049 (planned interim analysis)
- **Secondary outcomes:** breast symptom on other days, satisfaction, acceptability, side-effects

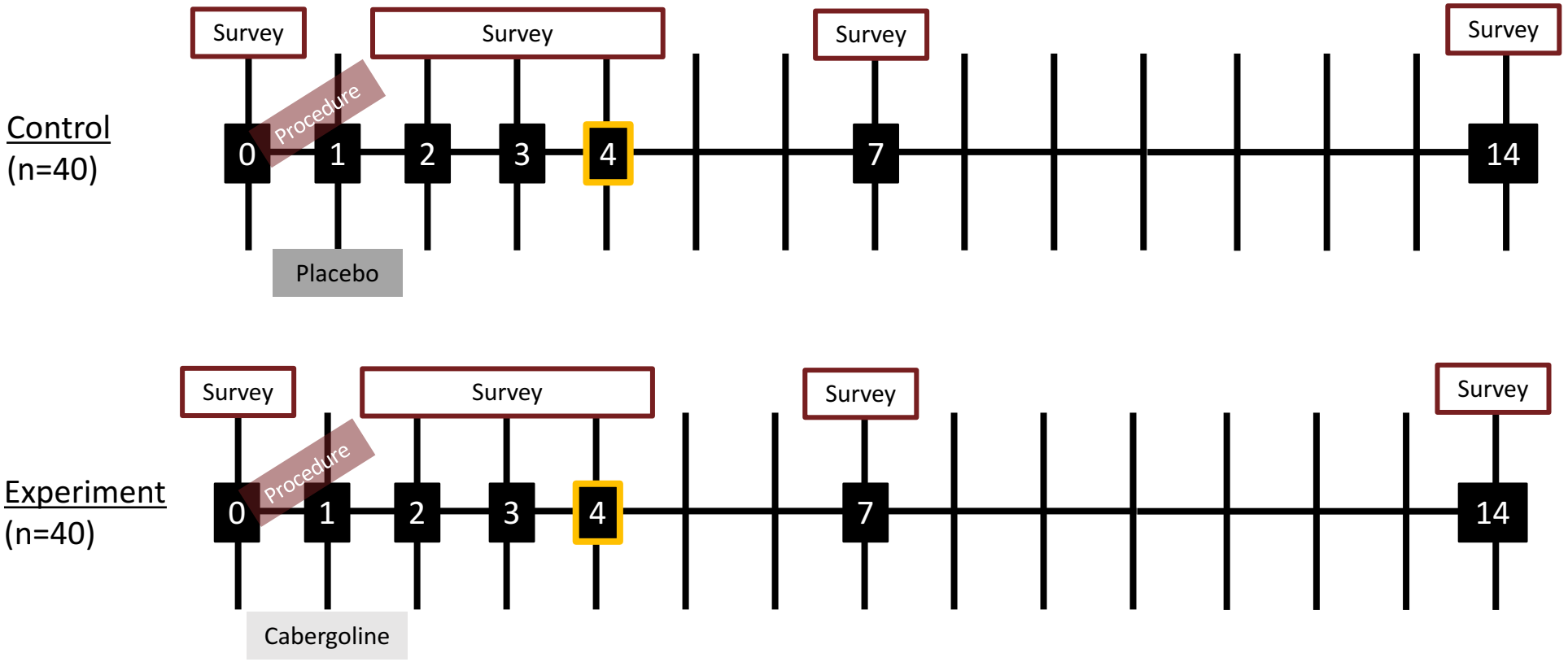
Rating Criteria of Bristol Record of Symptoms

Item	*Rating Criteria*
Breast engorgement	1 = Absence of symptoms (before breasts started to fill and after subsidence of symptoms)
	2 = Slight degree (breasts begin to fill or after they had been full and started receding)
	3 = Moderate degree (full breasts)
	4 = Severe degree (skin around breasts became obviously tight or swelling occurred under the arms where neither the binder nor bra could be effective)
Breast tenderness	1 = No complaint of tenderness voiced or elicited by palpation of, or by accidental pressure on, the breast
	2 = Tenderness occurs only on touch or pressure
	3 = Awareness of tenderness without touch (with or without a non-narcotic analgesic)
	4 = Tenderness requiring a narcotic for pain relief
Breast leakage	1 = Absence of any noticeable discharge
	2 = Slight (a drop or two and slight spotting on undergarments)
	3 = Moderate (periodic free and easy flow of milk or easy flow during a shower)
	4 = Severe or copious (several pads other than an ordinary tissue needed to absorb leakage and if changes are required several times during the day)
Pain relief[a]	1 = No other means needed other than breast binder or support bra
	2 = Ice bags used to obtain relief from breast tenderness
	3 = Use of nonnarcotic analgesic
	4 = Use of narcotic analgesic

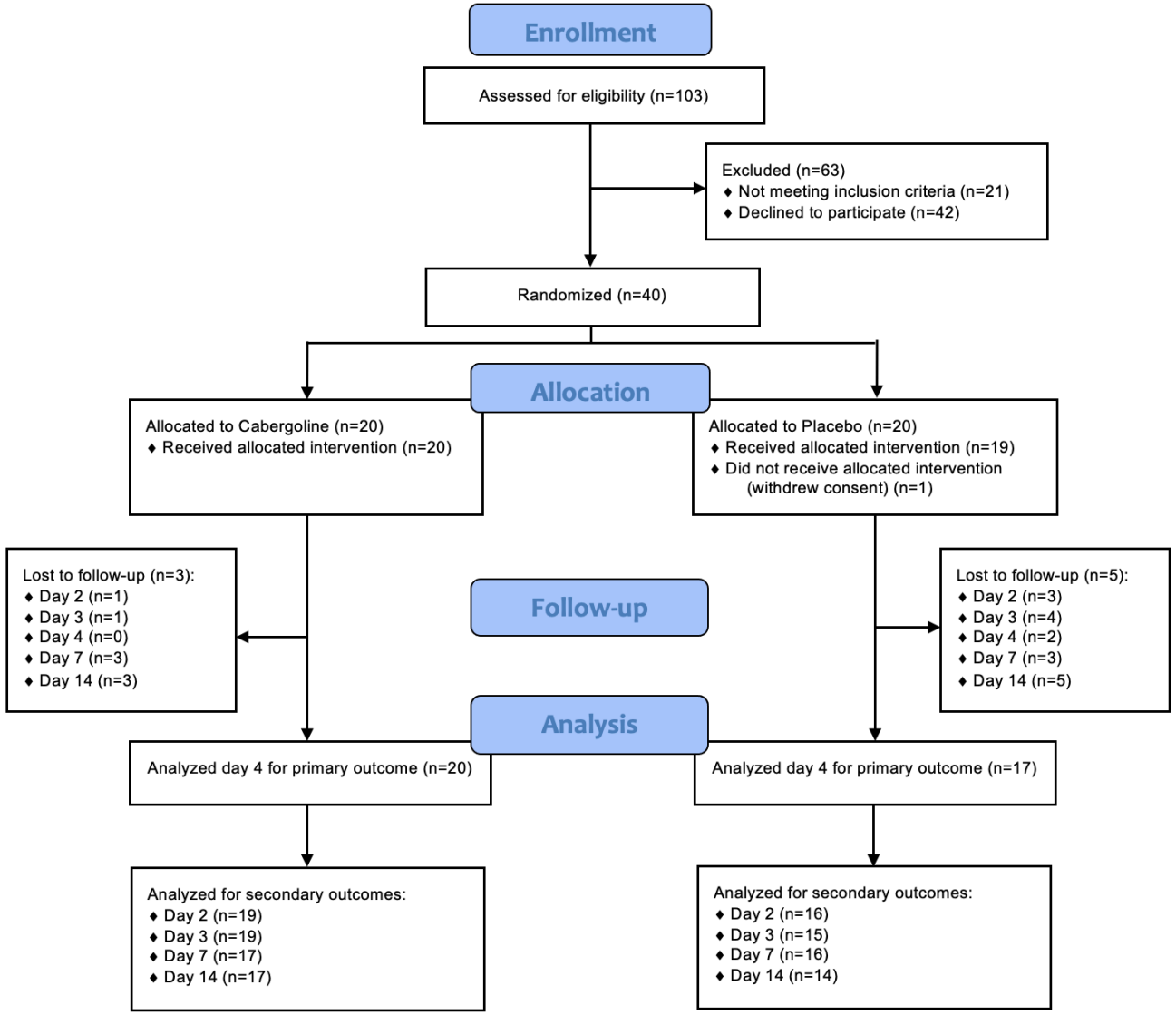
[a]Individuals received points for each use of a relief measure. For example, if the woman took acetaminophen on three occasions one day, she would get a score of 9 for that day.

Bristol WM. Comparative effectiveness of compressional and supporting breast binders in suppressing lactation. Nurs Res. 1966;15(3):203-6

Methods


Control
(n=40)
Survey
Survey
Survey
Survey
Procedure
0
1
2
3
4
7
14
Placebo
Experiment
(n=40)
Survey
Survey
Survey
Survey
Procedure
0
1
2
3
4
7
14
Cabergoline

Results


Enrollment
Assessed for eligibility (n=103)
Excluded (n=63)
♦ Not meeting inclusion criteria (n=21)
♦ Declined to participate (n=42)
Randomized (n=40)
Allocation
Allocated to Cabergoline (n=20)
♦ Received allocated intervention (n=20)
Allocated to Placebo (n=20)
♦ Received allocated intervention (n=19)
♦ Did not receive allocated intervention (withdrew consent) (n=1)
Lost to follow-up (n=3):
♦ Day 2 (n=1)
♦ Day 3 (n=1)
♦ Day 4 (n=0)
♦ Day 7 (n=3)
♦ Day 14 (n=3)
Follow-up
Lost to follow-up (n=5):
♦ Day 2 (n=3)
♦ Day 3 (n=4)
♦ Day 4 (n=2)
♦ Day 7 (n=3)
♦ Day 14 (n=5)
Analysis
Analyzed day 4 for primary outcome (n=20)
Analyzed day 4 for primary outcome (n=17)
Analyzed for secondary outcomes:
♦ Day 2 (n=19)
♦ Day 3 (n=19)
♦ Day 7 (n=17)
♦ Day 14 (n=17)
Analyzed for secondary outcomes:
♦ Day 2 (n=16)
♦ Day 3 (n=15)
♦ Day 7 (n=16)
♦ Day 14 (n=14)

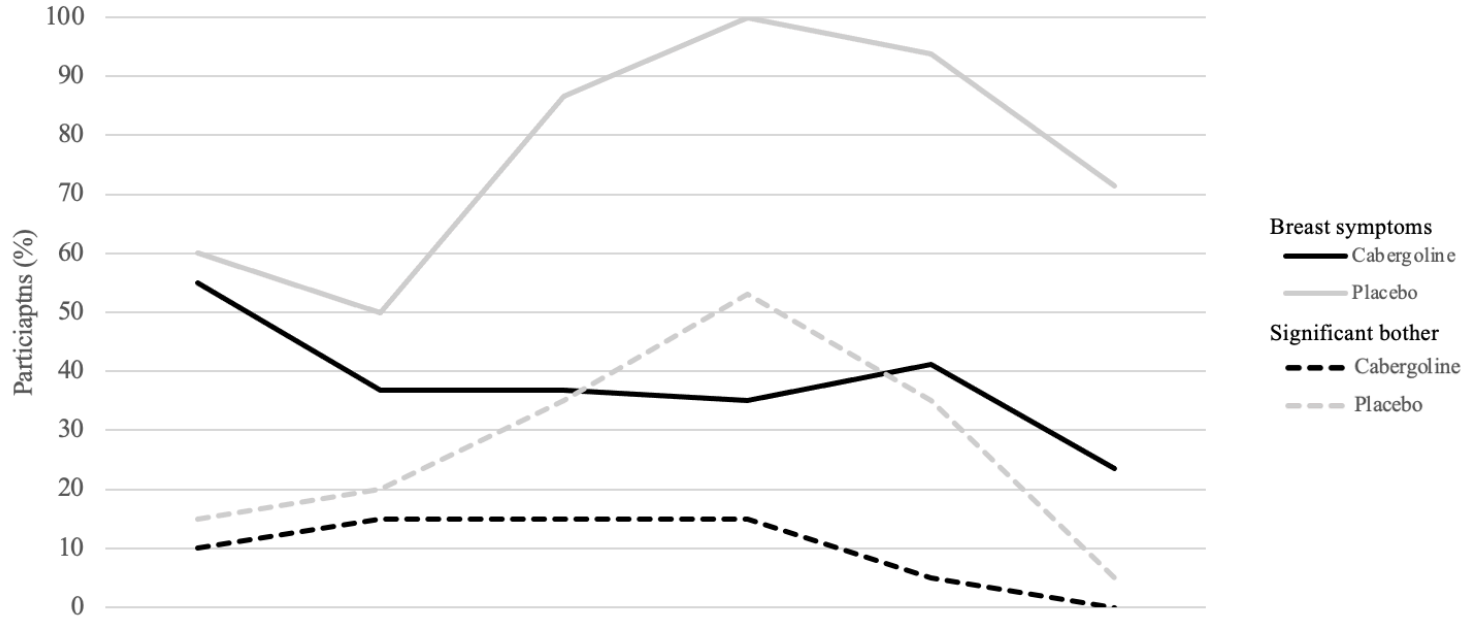
Results

Baseline characteristics

	Cabergoline (n=20)	Placebo (n=20)
Age	29.9±6.3	31.4±5.5
Parity	1 (0-4)	0 (0-4)
Nulliparous	9 (45)	15 (75)
Gestational age (days)	148.1+12.4	149.3±13.4
Gestational age (weeks)		
18w0d-19w6d	6 (30)	4 (20)
20w0d-21w6d	7 (35)	7 (35)
22w0d-23w6d	7 (35)	8 (40)
24w0d-28w0d	0 (0)	1 (5)
Indication		
Undesired pregnancy	10 (50)	3 (15)
Fetal anomaly	9 (45)	15 (75)
Maternal comorbidity	0 (0)	1 (5)
Fetal demise	1 (5)	1 (5)
Abortion method		
Procedural	18 (90)	17 (85)
Medication	2 (10)	3 (15)
Insurance		
Private	12 (60)	13 (65)
Medicaid	8 (40)	7 (35)
Self-pay	0 (0)	0 (0)
Gender		
Woman	19 (95)	20 (100)
Non-binary	1 (5)	0 (0)
Race		
White	7 (35)	11 (55)
Black	1 (5)	0 (0)
American Indian	0 (0)	1 (5)
Asian / Pacific Islander	8 (40)	7 (35)
Other	3 (15)	1 (5)
No response	1 (5)	0 (0)
Ethnicity		
Non-Hispanic	14 (70)	12 (60)
Hispanic	6 (30)	8 (40)
Prior breast surgery	1 (5)	0 (0)
Prior breastfeeding	8 (40)	6 (30)
Length of breastfeeding		
< 1 mo	1 (12.5)	0 (0)
1-6 mo	3 (37.5)	2 (33.3)
> 6 mo	4 (50)	4 (66.7)

Data are median (range), mean ± standard deviation, n (%)

Results



	Baseline	Day 2	Day 3	Day 4	Day 7	Day 14
Breast symptoms^						
Cabergoline	11/20	7/19	7/19	7/20	7/17	4/17
Placebo	12/20	8/16	13/15	17/17	15/16	10/14
p-value	0.75	0.43	**0.003**	**<0.0001**	**0.002**	**0.01**
Significant bother†						
Cabergoline	2/20	3/19	3/19	3/20	1/17	0/17
Placebo	3/20	4/16	7/15	9/17	7/16	1/14
p-value	1.0	1.0	0.14	**0.03**	**0.04**	1.0

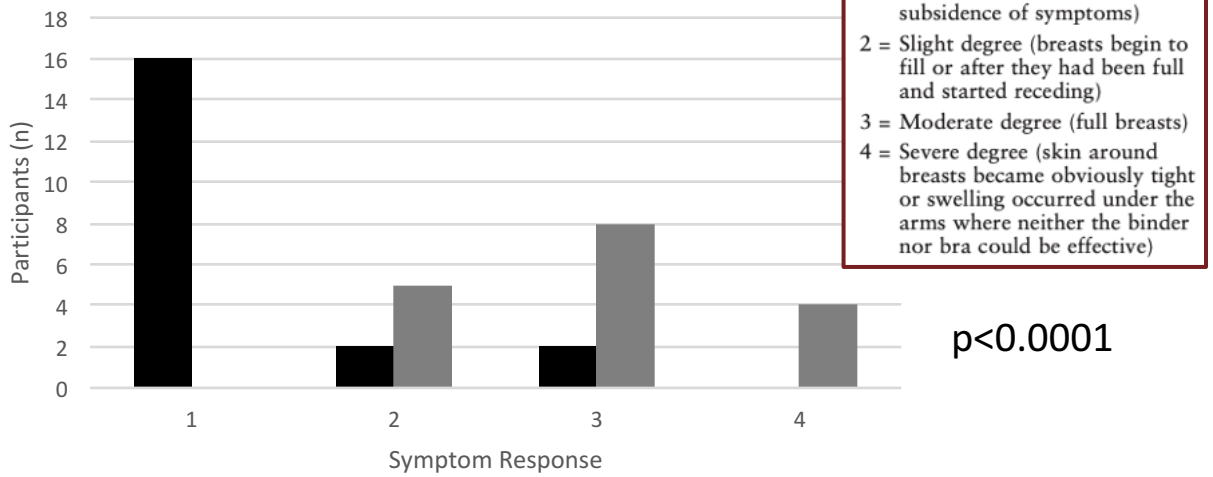
^Breast symptoms: Bristol Breast Symptoms Inventory assessed breast engorgement, tenderness, milk leakage, and need for pain relief modalities (scale range 1, absence of symptoms; 2-4 symptomatic). Any breast symptoms presented above is a score>1 in any of the four constructs assessing breast symptoms.
†Bother: Facial Pain Score (scale range: 0, not at all-6, extremely) used to assess bother from breast symptoms. Significant bother is those reporting a score $\geq$4 (a lot).

Results

Day 4 Breast Symptoms

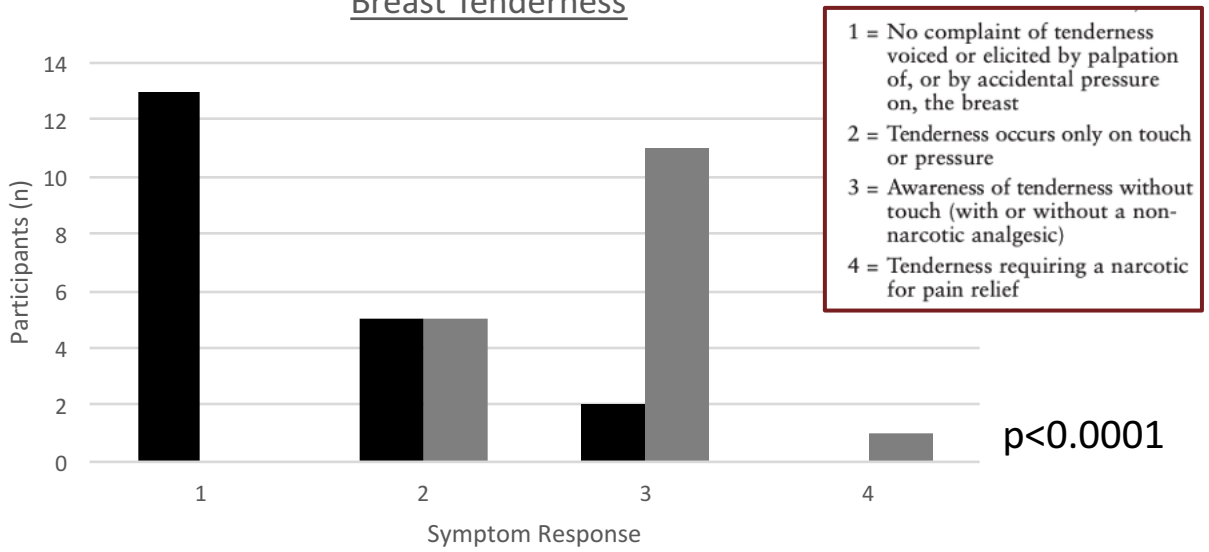
Cabergoline
Placebo

Engorgement



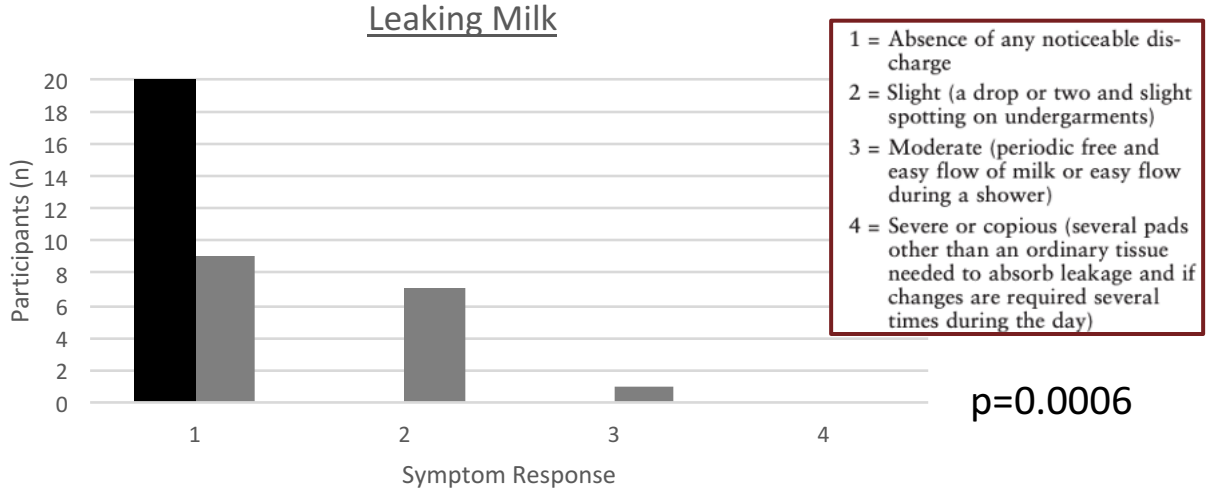
p<0.0001

Breast Tenderness



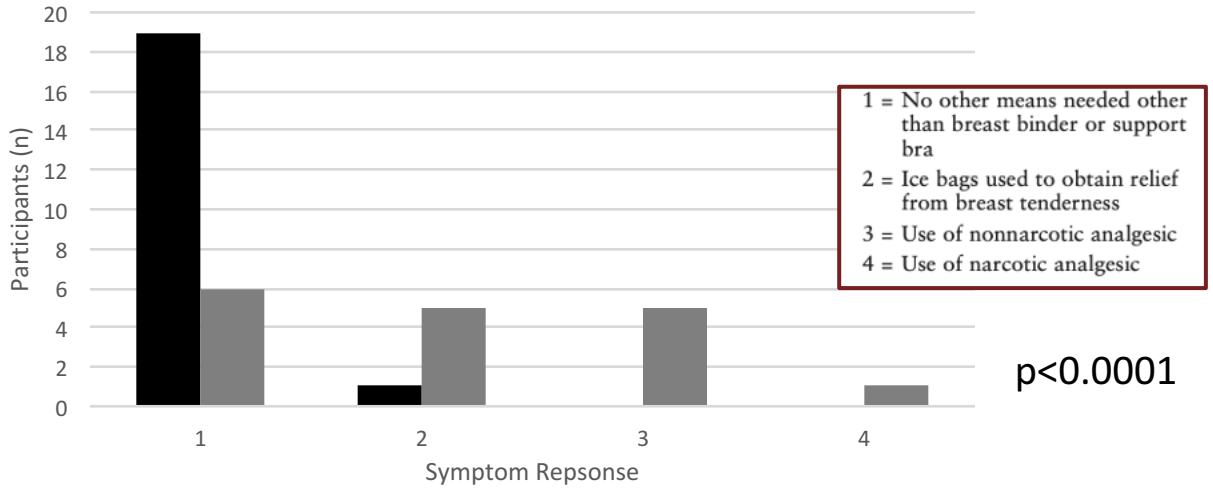
p<0.0001

Leaking Milk



p=0.0006

Pain relief



p<0.0001

^Breast symptoms: Bristol Breast Symptoms Inventory assessed breast engorgement, tenderness, milk leakage, and need for pain relief modalities (scale range 1, absence of symptoms; 2-4 symptomatic)

Results

Side effects

	No of adverse events		p-value
	Cabergoline (n=20)	Placebo (n=17)	
Nausea/ vomiting	4 (20)	1 (5)	0.34
Headache	7 (35)	4 (24)	0.48
Dizziness/ lightheadedness	3 (15)	1 (5)	0.61
Constipation	5 (25)	10 (59)	0.10
Acid reflux	2 (10)	2 (11)	1.0
Fatigue	3 (15)	6 (35)	0.45
Lower extremity edema	2 (10)	4 (24)	0.66
Hot flashes	0 (0)	5 (29)	**0.04**
Palpitations	0 (0)	1 (5)	1.0
Anxiety	2 (10)	1 (5)	1.0
Insomnia	4 (20)	4 (24)	1.0
Visual disturbance	1 (5)	0 (0)	1.0
Total reporting side-effects	14 (70)	15 (88)	0.46

Bother from Side-Effects

	Cabergoline	Placebo	p-value
Day 2	(n=19)	(n=16)	
Bother rating	0 (0-3)	0 (0-2)	0.08
Any bother	3 (33)	7 (70)	0.13
Significant bother	1 (5)	0 (0)	1.0
Day 3	(n=19)	(n=15)	
Bother rating	0 (0-2)	1 (0-3)	0.15
Any bother	6 (32)	8 (53)	0.20
Significant bother	0 (0)	2 (13)	0.19
Day 4	(n=20)	(n=17)	
Bother rating	0 (0-3)	1 (0-6)	0.11
Any bother	5 (25)	9 (53)	0.08
Significant bother	1 (5)	3 (18)	0.31
Day 7	(n=17)	(n=16)	
Bother rating	0 (0-4)	0 (0-4)	0.53
Any bother	5 (29)	6 (38)	0.62
Significant bother	1 (6)	3 (19)	0.33
Day 14	(n=17)	(n=14)	
Bother rating	0 (0-4)	0 (0-4)	0.75
Any bother	3 (18)	3 (21)	1.0
Significant bother	1 (6)	1 (7)	1.0

Bother on Facial Pain Score (0 = none, 6 = extremely); significant bother $\geq$4
Data are n (%), median (range)

Conclusions

- Breast engorgement is common after second-trimester abortion
- The severity of bother is under appreciated and under treated by most providers
- Recommended non-pharmacologic interventions: poor evidence for efficacy
- Pharmacologic intervention: existing safety data, emerging level 1 evidence for efficacy of cabergoline to prevent breast symptoms after 2nd trimester loss