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REVIEW

Is Cabergoline Safe and Effective for Postpartum Lactation Inhibition? A Systematic Review

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Background: Despite its benefits, there are some situations where breastfeeding is impossible or not recommended. Breast milk secretion and engorgement can be distressing to these non-breastfeeding women. There is currently no universal guideline on the most appropriate management for these women. Our objective is to evaluate the effectiveness and safety of cabergoline, a dopamine agonist, in lactation inhibition in postpartum women.

Methods: Studies were identified through electronic database searching (Cochrane library, EMBASE, Medline, IPA and Scopus) to identify all relevant studies that evaluated the use of cabergoline as a lactation inhibitor in postpartum women. Citations were screened and a narrative synthesis was undertaken given the heterogeneity of study designs.

Results: A total of six randomized trials met the inclusion criteria. Majority of the studies recruited healthy postpartum women electing for lactation inhibition for personal reasons. A range of 0.4 mg to 1 mg of cabergoline was given within 0 to 50 hrs of delivery. Dose–response relationship is established, and the highest rate of complete success was achieved with 1 mg of cabergoline, with time to cessation between 0 and 1 day. Cabergoline is non-inferior to bromocriptine for lactation inhibition while also associated with fewer rebound symptoms and adverse effects. Commonly reported adverse effects of cabergoline (eg, dizziness, headache and nausea) are self-limited.

Conclusion: Cabergoline is simple, effective and generally safe when given to postpartum women either wishing or needing to suppress lactation. Further research is needed to improve postpartum care of these women.

Keywords: cabergoline, dostinex, lactation suppression, lactation inhibition, postpartum

Background

There are many well-known benefits of breast milk for mother and infants; however, there are also instances that necessitate avoidance of breastfeeding. These may include the birth of a still born baby, neonatal death, maternal infection, such as HIV, which may be transmitted to the baby via breastmilk, and maternal illness that requires toxic therapy that may be excreted in the breastmilk.[1] According to the Canadian Community Health Survey in 2012, 11% of women do not breastfeed their newborn infants, and in 23% of cases it was because of a medical condition of the mother or child.[2] Women may also seek lactation inhibition for social or personal reasons. In the absence of breast stimulation from infant suckling, lactation will eventually cease in the span of days to weeks.[3] However, up to two-thirds of non-breastfeeding women may experience moderate to severe breast engorgement.[1] The physical pain can further compound the emotional pain in women who

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experienced fetal loss or sometimes grief over the inability to breastfeed. Breast binding, icing, fluid restriction, avoidance of tactile breast stimulation are techniques trialed in the past to help these women relieve physical symptoms; however, their efficacy is few and inconclusive.[1] Pharmacologic options such as estrogen preparations and bromocriptine are available. Their use is limited due to potential serious side effects such as cerebral accidents, myocardial infarction and postpartum psychosis.[4,5] Cabergoline is a newer synthetic ergoline that acts on the dopamine D2 receptors and is commonly used for the treatment of hyperprolactinemia. It has a Health Canada indication for "the prevention of the onset of physiological lactation in the puerperium for clearly defined medical reasons," but its use has not been adopted into routine practice in North America. For women living with HIV, there is a consensus in developed countries that exclusive formula feeding is recommended over breastfeeding in infants born to mothers with HIV. This is endorsed by the Society of Obstetricians and Gynaecologists of Canada (SOGC) 2014 guideline,[6] the Centers for Disease Control and Prevention (CDC) in the United States[7] and the British HIV Association (BHIVA).[8] Interestingly, the BHIVA 2018 guideline has a level 1C recommendation that cabergoline should be offered to suppress lactation in women not breastfeeding their infant by choice or who have high viral load >50 copies/mL.[8] The Royal College of Obstetricians and Gynaecologist (RCOG) in UK has discussed options for lactation suppression particularly for women experienced late intrauterine fetal death and stillbirth, and suggests that women should be advised that dopamine agonists successfully suppress lactation in a very high proportion of women and are well tolerated by a very large majority; cabergoline is superior to bromocriptine.[9] The purpose of this literature review is to evaluate the safety and effectiveness of cabergoline in lactation inhibition so that it may become a routine part of postpartum care for women in need of lactation inhibition.

Methods

We systematically reviewed studies that evaluated the use of cabergoline as a lactation inhibitor in postpartum women.

Search Strategy

Studies were identified through electronic database searching (Cochrane library, EMBASE, Medline, IPA and Scopus) in collaboration with a librarian at Neil John McLean Library, University of Manitoba. The search was updated until March 10, 2019. See Appendix for search detail (Prospero number CRD42019128987).

Inclusion and Exclusion Criteria

Studies eligible for inclusion were published in English or French, peer-reviewed, related to cabergoline and lactation inhibition, without publication date restrictions. Studies that focused on the use of cabergoline for other indications than lactation inhibition were excluded from the review, as were non-randomized controlled trials (RCT), editorials and clinical guidelines.

Citation Screening

Citations identified through our searches were exported to Zotero (https://www.zotero.org/). After de-duplication, titles and abstracts were screened independently by two authors. Articles were excluded based on the inclusion and exclusion criteria. All potentially includable papers underwent full-text review to ensure inclusion criteria were met. Any that did not were discarded prior to data extraction and analysis. See Figure 1 for PRISMA Flow Diagram for search and screening process.

Data Analysis

Studies were characterized according to their year of publication, research methodologies, participant attributes, interventions and types of outcome measured. Given the heterogeneity of study designs amongst studies and the limited number of studies on this subject, a statistical meta-analysis was not possible. We, therefore, conducted a narrative synthesis review. Risk of bias was assessed for each study using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions.[10]

Results

We have identified 140 articles from our primary search, of which 51 duplicates were removed. The remaining 89 articles were then subjected to abstract review and 16 of which were selected for full-text review. Finally, there were 6 RCT-based articles selected for data extraction and final discussion in this article. The results of these included studies are presented in Tables 1 and 2.

Overview of Available Literature

The 6 RCTs were mainly conducted in industrialized countries, including one large multicentre study conducted

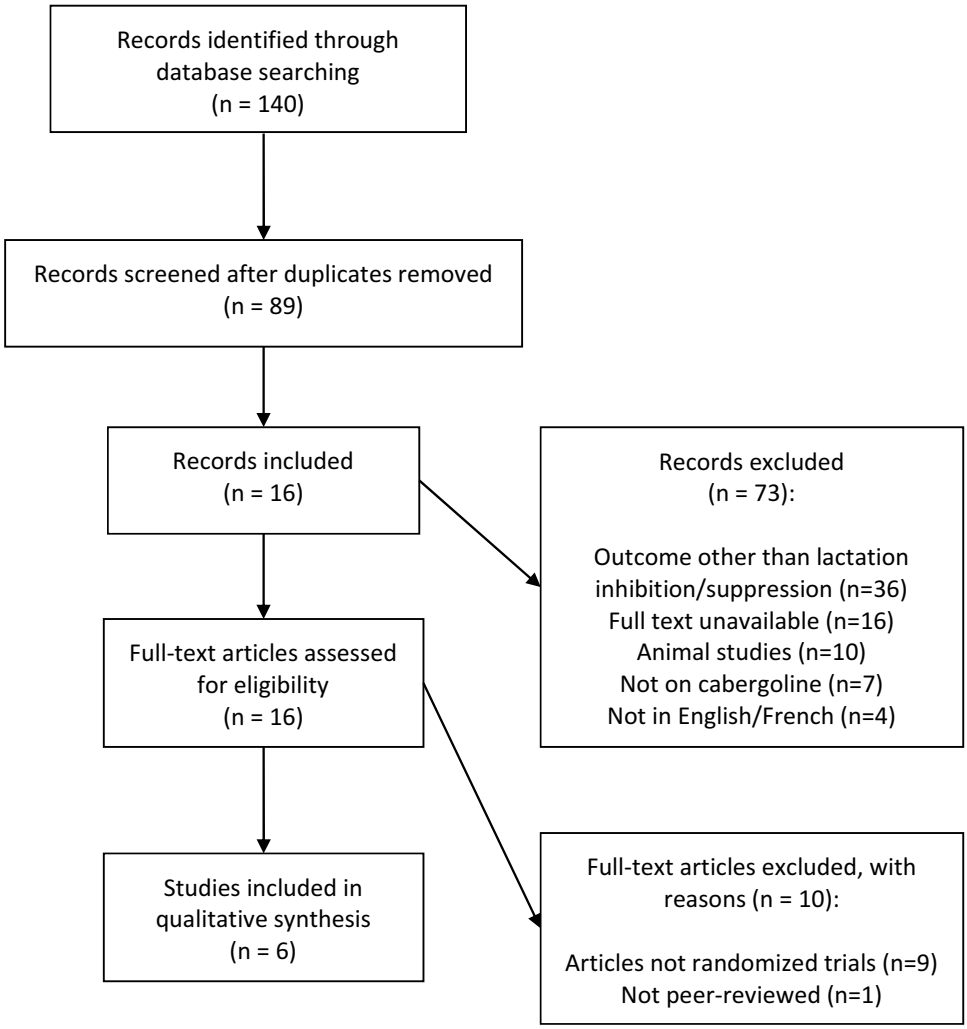

Figure 1 PRISMA flow diagram.

in Europe.[11] Studies were published between 1987 and 2009.

Participant Attributes

Between all studies, a total of 693 participants had been recruited. Exclusion criteria were specified for few studies including women with a history of hypersensitivity to ergot alkaloids, essential hypertension, pre-eclampsia, hepatic or renal disorder, history of agalactia or hypogalactia and patients who underwent treatments of another disorder that may interfere with prolactin secretion.[11,12] The most common reason for lactation inhibition was "personal reasons." One study had recruited participants who were unable to breastfeed due to stillbirth or neonatal death.[13] The European Multicentre study also recruited women who had medical contraindications to breastfeeding but did not elaborate beyond.[11]

Interventions

Four studies have compared cabergoline with placebo;[12,14–16] one study has compared cabergoline with bromocriptine[14] and one study compared cabergoline with estrogen–androgen combination.[13] Cabergoline was administered orally as a one-time dose in all of the studies for lactation inhibition with doses ranging between 0.4 and 1 mg. Nisha et al had additionally used a 0.25 mg twice a day for 2 days as dosing regimen for women with already-established lactation.[13] Majority of the studies have commenced treatments shortly after delivery within 24 hrs, the longest being 50 hrs postdelivery.[14]

Outcome Assessment Methods

Assessment of outcomes was variable amongst the studies. Two studies utilized daily self-administered questionnaires during in-hospital stay[11,15] regarding symptoms of lactation,

Table 1 Study Demographics and Methodologies

Study	Study Design	Participants	Comparator Groups		Cabergoline Given
Caballero-Gordo et al, 1991[12] Spain	Prospective, randomized, double-blind controlled trial.	140 healthy postpartum women Reasons: did not wish to BF or unable to Exclusion criteria: history of agalactia, drug allergy, stillbirth, hepatic or renal disorders, those undergoing treatment that may interfere with prolactin secretion	Interventions: Cabergoline 0.5mg (n=40) Cabergoline 0.75mg (n=40) Cabergoline 1mg (n=40)	Control: Placebo (n=20)	<24 hrs after delivery
European Multicentre Study Group for Cabergoline in Lactation Inhibition, 1991[11] 12 European Centers	Prospective, randomized, double-blind trial.	272 healthy postpartum women Reasons: Personal and medical reasons (did not elaborate) Exclusion criteria: history of agalactia or hypogalactia, drug allergy, intrauterine fetal death, pre-eclampsia, hepatic or renal impairment and those with concomitant acute diseases	Interventions: Cabergoline 1mg (n=136)	Control: Bromocriptine 2.5 mg twice daily for 14 days (n=136)	<27 hrs after delivery
Giorda et al, 1991[14] Italy	Prospective, randomized single-blind controlled trial	36 healthy postpartum women Reasons: Personal reasons	Interventions: Cabergoline 1 mg (n=18)	Control: Bromocriptine (n=18) Placebo (n=13)	50 hrs after delivery
Melis et al, 1987[15] Italy	Prospective, randomized single-blind controlled trial	17 healthy postpartum women Reasons: Personal reasons	Interventions: Cabergoline 0.4 mg (n=7) Cabergoline 0.6 mg (n=5)	Control: Placebo (n=5)	24-48 hrs after delivery
Melis et al, 1988[16] Italy	Prospective, randomized, double-blind controlled trial.	32 healthy postpartum women Reasons: Personal reasons Exclusion criteria: use of general anaesthetic agents	Interventions: Cabergoline 0.4 mg (n=8) Cabergoline 0.6 mg (n=8) Cabergoline 0.8 mg (n=8)	Control: Placebo (n=8)	<24 hrs after delivery
Nisha et al, 2009[13] India	Prospective, randomized controlled trial	196 healthy postpartum women Reasons: Stillborn (inhibition), neonatal death (suppression)	Interventions: Cabergoline1mg for inhibition (n=54) Cabergoline 0.25mg twice daily for 2 days for suppression (n=46)	Control: 1 IM injection up to 3 of estrogen-androgen combo for inhibition (n=48) and for suppression (n=48)	<24 hrs after delivery or neonatal death

while four studies utilized a combination of interview and daily breast examinations conducted by healthcare providers.[12–14,16] The major parameters of breast symptoms sought for include milk secretion, breast pain and engorgement. Treatment success was determined on various end observation periods with some on day 3[11] on day 4,[15] on day 14[12,14,16] as well as one chosen the endpoint to be "no milk expression even on pressing of the breasts"[13] The definition for "successful treatment" also varied, some studies allow mild spontaneous milk secretion,[11] while others require a complete absence of any breast symptoms including secretion, tenderness or engorgement.[12,14]

Efficacy Outcome Measures

Cabergoline vs Placebo

Three studies have demonstrated a linear dose–response relationship for cabergoline on lactation inhibition, with the lowest effective dose being 600 mcg (see Table 2).[12,15,16] Caballero-Gordo et al randomized 140 healthy puerperal women to 0.5 mg, 0.75 mg, 1 mg of cabergoline or placebo given within 24 hrs of delivery. The percentages of participants with no breast symptoms up to postpartum day 14 were 90% (n=36), 62.5% (n=28), 45% (n=18) and 20% (n=4), respectively, for 1 mg, 0.75 mg, 0.5 mg cabergoline and placebo.[12] The differences were statistically significant with regard to each group.[12]

Table 2 Study Outcomes

Study	Outcome Assessment Method	Efficacy Outcome	Cessation (Days)	Safety Outcome
Caballero-Gordo et al, 1991[12] Spain	Interview and physical examination daily for 5 days; subsequent self-administered questionnaire after discharge; return on day 14 for final examination	90%, 70%, 45%, 20% of participants received 1mg, 0.75mg, 0.5mg and placebo respectively had no breast symptoms during hospitalization or up to day 14. Statistically significant between all four groups ($p<0.01$)	Not reported (n.b women that received additional1mg of cabergoline had symptoms completely disappeared within 2 days)	Dizziness (n=2), 0.75 mg and 1 mg H/A (n=1), 1 mg Dizziness and H/A (n=1), 1 mg * occurred before day 1–3, mild and self-limiting. NOTE: no difference in BP noted between different subgroups
European Multicentre Study Group for Cabergoline in Lactation Inhibition, 1991[11] 12 European Centers	Self-administered questionnaire daily during hospital stay (at least 3days); subsequent questionnaire on return visit or home visit on day 15; subsequent visit or telephone call on day 21. Treatment success evaluated on day 3 and day 15.	78% and 69% of cabergoline and bromocriptine group respectively had no breast symptoms on day 14. Not statistically significant. 4% and 17% of cabergoline and bromocriptine group respectively had rebound breast symptoms. ($p<0.0001$)	Not reported	Cabergoline group had 25 adverse events in n=22 (Dizziness and H/A most common) Bromocriptine had 44 adverse events in n=36 (Dizziness and nausea most common) Serious side effects: dizziness (n=1), vertigo (n=1), symptomatic hypotension (n=1) in bromocriptine group. none in cabergoline group Unexplained side effects: cabergoline: epistaxis (n=1), transient hemianopia (n=1) bromocriptine: facial paralysis (n=1), precordial pain (n=1), fever (n=1), vaginal hemorrhage (n=1)
Giorda et al, 1991[14] Italy	Interviews and physical examination every other day for first week and on day 14 from start of treatment	94% and 89% of cabergoline and bromocriptine group respectively had no breast symptoms at day 14	Not reported	Cabergoline: Dizziness (n=3), headache (n=1), vomit (n=1) Bromocriptine: transient amaurosis (n=1, unknown origin), dizziness (n=1), nausea (n=4), H/A-nausea (n=4), dizziness-nausea (n=1), H/A (n=3)
Melis et al, 1987[15] Italy	Self-administered questionnaire daily for 4 days	0%, 43% and 100% of placebo, 400mcg and 600mcg cabergoline respectively had no breast symptoms on day 4	Not reported	Asymptomatic orthostatic hypotension (n=1), cabergoline with no specified dosage
Melis et al, 1988[16] Italy	Interviews and physical examination daily for 4 days and on day 14 post treatment	13%, 50%, 100% and 100% of placebo, 400mcg, 600mcg and 800mcg cabergoline respectively no breast symptoms on day 14	0–1	No side effects were observed in this study (No nausea, vomiting, hypotension, nasal stuffiness)
Nisha et al, 2009[13] India	Interviews and physical examination daily until no milk expression even on pressing the breasts	100% and 98% success inhibition with cabergoline and estrogen–androgen combination. ($p=0.286$) 96% and 79% successful suppression with cabergoline and estrogen–androgen combination ($p=0.017$) 4% of cabergoline for suppression compared to 21% for estrogen-androgen combination required extra doses	Cabergoline: 0.73 day for inhibition and 3.29 days for suppression Estrogen–androgen combination: 1.81 days for inhibition and 3.96 days for suppression	Not reported

Melis et al randomized 17 healthy puerperal women to 400 mcg cabergoline, 600 mcg cabergoline or placebo given within 24–48 hrs of delivery.[15] By day 2 after treatment, all five women in the placebo group had evident engorgement and were subsequently given bromocriptine and excluded from the study thereafter.[15] Forty-three percent (n=3) and 100% (n=5)

of those received 400 mcg and 600 mcg cabergoline, respectively, had no signs of lactation or breast engorgement throughout the observation period.[15] Melis et al, in another study, randomized 32 healthy postpartum women to 0.4 mg, 0.6 mg, 0.8 mg of cabergoline or placebo given within 24 hrs of delivery and found that lactation was completely prevented in subjects receiving 600 mcg and 800 mcg of cabergoline. Half of the subjects receiving 400 mcg cabergoline had complete success. In the placebo group, only one woman showed no signs of lactation during the 14-day observation period.[16]

Cabergoline vs Bromocriptine

The European multicenter study and Giorda et al have both reached the same conclusion that 1 mg of cabergoline given as a single oral dose is non-inferior to 5 mg daily for 14 days of bromocriptine in preventing puerperal lactation.[11,14] The European multicenter study demonstrated that if a difference does exist between the two compounds, it is unlikely to be more than 10% ($p<0.001$).[11] Complete success where there is absence of any breast signs other than mild spontaneous milk secretion on day 14 was achieved in 78% (n=106) of participants receiving cabergoline versus that of 69% (n=94) for bromocriptine.[11] Giorda et al reported a slightly higher efficacy for both groups where 94% (n=17) and 89% (n=16) of participants in the cabergoline and bromocriptine group, respectively; had absence of secretion, engorgement or tenderness on day 14.[14]

Time to Effect and Duration of Effect

The time to lactation inhibition in those reported was less than 1 day. For those with established lactation, cabergoline on average required 3.29 days to stop.[13] In Caballero-Gordo et al, where participants who failed an initial dose of cabergoline 1 mg and then received an additional 1 mg dose, symptoms disappeared completely within 48 hrs.[12] The European multicenter study was the only one that had examined rebound lactation as one of the outcomes and found significantly fewer ($p<0.0001$) participants with rebound breast symptoms on day 21 in the cabergoline (5%, n=5) versus bromocriptine group (24%, n=23).[11]

Lactation Inhibition vs Suppression

Nisha et al was the only study that had made a clear distinction between inhibition (i.e., preventing the onset of lactation) and suppression (i.e., stopping established lactation). They have used different dosing regimens for the two purposes. The authors found that the mean number of days required for inhibition of lactation was fewer in the cabergoline group compared to those receiving the estrogen–androgen combination (0.73±0.963 days vs 1.81±1.81 days, $p=0.001$).[13] The mean number of days required for lactation suppression between cabergoline and estrogen–androgen combination was not statistically significant (3.29±2.59 days vs 3.96±2.81 days, $p=0.244$).[13] Preventive efficacy of cabergoline vs estrogen–androgen combination was 100% vs 98%, respectively ($p=0.286$).[13] Suppressive efficacy was 96% vs 79%, respectively ($p=0.017$).[13]

Safety Outcome Measures

Overall Safety of Cabergoline

Safety outcomes were reported in all but one of the six studies,[13] and results are presented in Table 2. Three studies have reported <10% of the participants experienced side effects (0%,[16] 3%,[12] 8%[15]). More specifically, Caballero-Gordo et al reported that 3% (n=4) of participants had dizziness and headaches that were mild and self-limiting.[12] No significant differences were reported between different doses (0.5 mg, 0.75 mg, 1 mg) of cabergoline and placebo in systolic and diastolic blood pressures of the participants.[12] In the study by Melis et al who examined 17 healthy postpartum women, one individual had asymptomatic orthostatic hypotension 3–6 hrs after the administration of cabergoline with a drop of 15 and 5 in SBP and DBP, respectively.[15] None of the individuals had symptomatic hypotension and also no major side effects were found in this study.[15] Melis et al, in a separate study, had found that of the 32 healthy puerperal women, no side effects were observed in participants that received cabergoline.[16] More specifically no nausea, vomiting, hypotension or nasal stuffiness were reported.[16]

Two studies have reported >10% of participants experienced side effects (16%[11] and 28%[14]). The European multicenter study has reported adverse effects in 16% (n=22) of cabergoline-treated individuals in contrast to 26% (n=36) of bromocriptine-treated individuals.[11] Majority of the side effects occurred early after drug administration and tapered down after the first 3–4 days.[11] Interestingly, this study found 2 individuals in the cabergoline group had unexplained side effects including epistaxis and transient hemianopia, and 4 individuals in the bromocriptine group experienced facial paralysis, precordial pain, fever and vaginal hemorrhage.[11] Whether or not these symptoms were related to the 2 compounds is unknown as there were no such prior events described.[11] Giorda et al enrolled 36 healthy postpartum women who underwent cesarean section and randomized them equally to receive either cabergoline or bromocriptine for lactation inhibition.[14] He had reported

28% (n=5) and 78% (n=14) of individuals received cabergoline and bromocriptine, respectively, had developed adverse effects.[14] More specifically, 3 individuals of the cabergoline group experienced dizziness after administration, 1 with headache and 1 with vomiting.[14] The authors believed the individual with vomiting may have been due to laparotomy rather than cabergoline. All of the reported adverse events resolved spontaneously with the exception of one individual with headache that required analgesic.[14] This is in contrast to the bromocriptine treatment group where 1 individual experienced transient amaurosis of unknown origin, 1 had dizziness, 9 had nausea, and 4 had headaches.[14] The majority of these also spontaneously resolved however some required dosage adjustment. The reported duration of side effects was between 5 mins to 5 days and 3 mins to 14 days in the cabergoline and bromocriptine groups, respectively.[14]

Overall, these results consistently indicate that cabergoline, given as a single dose for lactation inhibition, is safe and is associated with only minor, self-limiting side effects. Cabergoline has a more favorable safety profile than bromocriptine.

Potential Risk of Bias

We have utilized Cochrane Collaboration's tool for assessing the risk of bias.[10] See Figure 2 for summary and Table 3 for details of each study. With regard to the risk of selection bias, only two studies[11,14] have clearly stated the use of a random number table, with all other studies simply stating that the participants were "randomized," but no methods of sequence generation were described.[12,13,15,16] Three studies have reported methods of allocation concealment with the use of "double-dummy technique" in the European study to make up the differences in treatment lengths in different arms,[11] and the use of identical vials containing lyophilized powder of cabergoline and placebo in the Melis 1988 study[16] and use of sealed envelope containing instructions for different treatment arms in Nisha et al.[13] With regard to blinding, three studies had used a double-blind approach and therefore considered low risk.[11,12,16] Two studies (Giorda et al and Melis et al) were conducted in a single-blind fashion.[14,15] and one study (Nisha et al) was not blinded.[13] Overall, we considered all 6 trials to be at low risk of attrition bias. The European study had 5% non-adherence to the protocol, some were due to intolerance, lost to follow up and other non-specified reasons.[11] Furthermore, the same had 34 total participants out of 272 that had received concomitant treatment that may interfere with lactation such as ergot derivatives and oral contraceptives.[11] For the three studies with reported exclusion criteria, one study had excluded those undergoing treatment that may interfere with prolactin secretion,[12] another one had excluded those with concomitant acute disease.[11] Overall, given the ease of administration of cabergoline, the

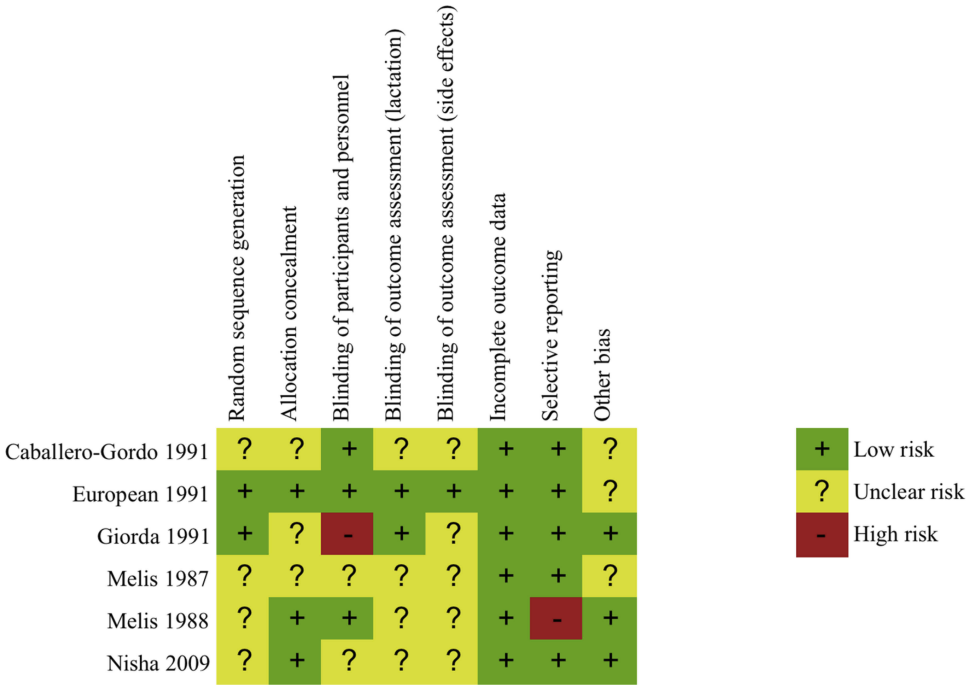

Figure 2 "Risk of bias" summary.

Table 3 Risk of Bias Assessments

Bias	Author's Judgement	Support for Judgement
Caballero-Gordo et al, 1991[12]		
Random sequence generation	Unclear risk	Quote: "the study was prospective, randomized and double blind" Comment: Randomization process not stated
Allocation concealment	Unclear risk	Quote: "the study was prospective, randomized and double blind" Comment: Allocation concealment not stated
Blinding of participants and personnel	Unclear risk	Quote: "double blind" Comment: Insufficient information to judge
Blinding of outcome assessment (lactation)	Unclear risk	Quote: "double blind" Comment: Subjective outcomes may be more vulnerable to bias
Blinding of outcome assessment (side effects)	Unclear risk	Quote: "double blind" Comment: Subjective outcomes may be more vulnerable to bias
Incomplete outcome data	Low risk	Quote: "9 patients were excluded because of protocol violations, 6 because they did not return for an examination at 14 days and 3 because they used bromoergocryptine after treatment" Comment: 1/20 placebo, 3/40 0.50mg, 4/40 0.75mg and 1/40 1mg group were excluded
Selective reporting	Low risk	Comment: No evidence of selective reporting
Other bias	Unclear risk	Comment: Number of participants in placebo group were only half of other intervention groups
European Multicentre Study Group for Cabergoline in Lactation Inhibition, 1991[11]		
Random sequence generation	Low risk	Quote: "subjects randomised". Treatments given "according to a randomised sequence balanced within each centre"
Allocation concealment	Low risk	Quote: "treatments were given double blind, using the double dummy technique" "the drugs were provided … in individualized patient kits, which were assigned by the doctor according to the patient's order of entry to the study"
Blinding of participants and personnel	Low risk	Quote: "treatments were given double blind, using the double dummy technique" "in one instance the code was broken before the end of the study for one woman taking cabergoline owing to an unexpected adverse event (hemianopia), the women remained blind to the treatment" Comment: Double-blind, and unlikely that the blinding could have been broken
Blinding of outcome assessment (lactation)	Low risk	Comment: Placebo was used to make up for the difference in the duration of treatments between the 2 arms of the trial
Blinding of outcome assessment (side effects)	Low risk	Quote: "treatments were given double blind"
Incomplete outcome data	Low risk	6/136 missing from cabergoline group (1 due to "intolerance", 2 due to "lost to follow up", 3 due to "other reasons"); 8/136 missing from bromocriptine group (3 due to "intolerance", 3 due to "lost to follow up", 2 due to "other reasons") Comment: Subjects not completing the study protocol were included in analysis as "treatment failure". Missing data balanced across groups and reasons similar
Selective reporting	Low risk	Comment: No evidence of selective reporting
Other bias	Unclear risk	18/136 taking cabergoline and 16/136 taking bromocriptine received concomitant treatment that may have interfered with lactation (ergot derivatives in 28 and oral contraceptives in 6, equally dispensed over the 2 groups)

(*Continued*)

Table 3 (Continued).

Bias	Author's Judgement	Support for Judgement
Giorda et al, 1991[14]		
Random sequence generation	Low risk	Quote: "the women were randomly allocated with random tables"
Allocation concealment	Unclear risk	Comment: Allocation concealment not described
Blinding of participants and personnel	High risk	Quote: "single-blind"
Blinding of outcome assessment (lactation)	Low risk	Quote: "breast engorgement, breast tenderness and milk secretion were assessed clinically by one of us unaware of the type of treatment who recorded the presence or absence of these variables"
Blinding of outcome assessment (side effects)	Unclear risk	Quote: "clinical side effects reported by the women either spontaneously or after specific questions were also recorded" Comment: subjective
Incomplete outcome data	Low risk	Comment: No missing data
Selective reporting	Low risk	Comment: No evidence of selective reporting
Other bias	Low risk	Comment: No other sources of bias
Melis et al, 1987[15]		
Random sequence generation	Unclear risk	Quote: subjects were "randomly divided into 3 treatment groups in a single blind fashion" Comment: Randomization process not stated
Allocation concealment	Unclear risk	Comment: No information about allocation concealment to permit judgement
Blinding of participants and personnel	Unclear risk	Comment: Insufficient information to permit judgement on blinding. Study was labeled as "single blind", unclear who was blinded and the measure taken to ensure blinding
Blinding of outcome assessment (lactation)	Unclear risk	Comment: Insufficient information to permit judgement on blinding. Study was labeled as "single blind", unclear who was blinded and the measure taken to ensure blinding
Blinding of outcome assessment (side effects)	Unclear risk	Comment: Insufficient information to permit judgement on blinding. Study was labeled as "single blind", unclear who was blinded and the measure taken to ensure blinding
Incomplete outcome data	Low risk	Comment: No missing data
Selective reporting	Low risk	Comment: No evidence of selective reporting
Other bias	Unclear risk	Comment: Insufficient information to assess
Melis et al, 1988[16]		
Random sequence generation	Unclear risk	Quote: "subjects were randomly allocated to four treatment groups of eight subjects" Comment: Randomization process not stated
Allocation concealment	Low risk	Quote: "the three doses of Cabergoline and placebo were supplied in identical vials containing a lyophilized powder, which was restored to a liquid state with water immediately before use"
Blinding of participants and personnel	Low risk	Quote: "double blind trial" "neither the patients nor the staff administering the solutions were aware of which treatment was being given"
Blinding of outcome assessment (lactation)	Unclear risk	Comment: Unclear whether outcome assessors were blinded

(*Continued*)

Table 3 (Continued).

Bias	Author's Judgement	Support for Judgement
Blinding of outcome assessment (side effects)	Unclear risk	Comment: Unclear whether outcome assessors were blinded
Incomplete outcome data	Low risk	Comment: No missing data
Selective reporting	High risk	Quote: "No nausea, vomiting, hypotension, or nasal stuffiness were reported by the subjects who received Cabergoline" Comment: method of measuring side effect measurement was not pre-specified in the methods section. Unclear if there were other side effects sought for but not reported. Unclear if placebo groups had any side effects.
Other bias	Low risk	Comment: No other sources of bias
Nisha et al, 2009[13]		
Random sequence generation	Unclear risk	Quote: "they were randomly divided into two groups" Comment: Randomization process not stated
Allocation concealment	Low risk	Quote: "a total of 200 opaque white envelopes were sealed, mixed and put in a box" "each woman was asked to open one envelope and recruited in one of the two groups as per instructions inside the envelope"
Blinding of participants and personnel	Unclear risk	Comment: No blinding, route of administration was different between the 2 comparison groups (oral form versus IM injection)
Blinding of outcome assessment (lactation)	Unclear risk	Comment: No blinding
Blinding of outcome assessment (side effects)	Unclear risk	Comment: The study did not address this outcome
Incomplete outcome data	Low risk	Comment: No missing data
Selective reporting	Low risk	Comment: No evidence of selective reporting
Other bias	Low risk	Comment: No other sources of bias

protocol adherence rate was high across the studies. In terms of selective reporting, we considered all but one trial to be at low risk. Melis et al 1988 had reported "no nausea, vomiting, hypotension or nasal stuffiness reported by the subjects who received cabergoline," specific symptoms sought for were not prespecified in the "Methods" section.[16] Three studies appear free of other bias.[13,14,16]

Discussion

Narrative Review Summary

This narrative review is the first study to focus solely on cabergoline's efficacy and safety in lactation inhibition. It can be given as 1 mg within 24 hrs postpartum and has a rapid onset of action of 1 day. The most common reported side effects include dizziness, headaches and nausea that occurs mainly in the first 3 days post-treatment and tapers afterward. Cochrane has published a review in 2012 that consists of 62 controlled trials (6428 mothers) on treatments of lactation suppression.[4] Of those, 30 trials investigated bromocriptine compared to only 5 trials investigated cabergoline. Two studies included in this paper were not part of that review.[13,15] The Cochrane review has concluded weak evidence that some pharmacologic treatments (i.e., bromocriptine and estrogen preparations) are better than no treatment in lactation suppression.[4] No specific conclusions about cabergoline were drawn in that review. The Royal College of Obstetricians and Gynaecologist (RCOG) in UK published a green-top guideline that suggest for women experienced late intrauterine fetal death and stillbirth women should be advised that dopamine agonists successfully suppress

lactation in a very high proportion of women and are well tolerated by a very large majority; cabergoline is superior to bromocriptine.[9] Our findings in this review are in support of that recommendation.

Limitations of Current Studies and Future Direction

One major limitation of this review is that the studies included mostly consist of small trials. Larger randomized controlled trials would be required to detect clinically important side effects between treatment groups; however, given the infrequency with which inhibition of lactation is desirable, designing a study with an adequate sample-size would be challenging. There are also large variations in dosages, methods of data collection and outcome assessments. Perhaps utilizing both questionnaires and breast exams conducted by healthcare providers would reduce bias. A more consistent definition of lactation inhibition and suppression as well as treatment success would be helpful.

Furthermore, choices regarding infant feeding are very personal subjects. Often the reasons for not breastfeeding may be related to stillbirth, neonatal death or maternal illness, but the choice of not breastfeeding can be related to more personal reasons. Therefore, the underlying emotional aspect deserves attention as well. For instance, in cultures such as in Malawi, engorged and dropping breasts were seen as social taboos as it is thought to bring future illness to mother and child.[18] None of the studies have assessed patient satisfaction as an outcome, more studies should consider the acceptability of the treatment to be one of the outcome measures.

Although studies included in this review did not assess or report the incidence of psychosis post-cabergoline administration, there have been a few case reports of psychosis and mania associated with its use.[17] However, these were in non-pregnant population of which cabergoline was used for treatment of pituitary prolactinomas. The time taken for onset or worsening of psychiatric symptoms was greater than 1 month in the majority, and that for improvements was 1 week to 1 month post-cessation of cabergoline.[17] Nevertheless, prescribers need to be aware of this rare potential adverse effect and increased mental health monitoring during the early postpartum periods may be helpful.

Conclusion

Non-pharmacologic methods for lactation inhibition lack evidence in efficacy. Currently available pharmacologic agents such as bromocriptine are not ideal given its lengthy administration and potential serious side effects. Postpartum women who are unable to breastfeed can suffer pain from engorgement as well as emotional distress. This review evaluated the effectiveness and safety of cabergoline in puerperal lactation inhibition and has demonstrated that a single dose of 1 mg cabergoline given soon after delivery is effective and generally safe in postpartum women. However, careful consideration of risk is necessary particularly in the setting of psychiatric population. Vigilance is still needed in prescribing cabergoline for lactation inhibition.

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Disclosure

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