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Review

Comparing pyridoxine with dopaminergic agonists (cabergoline and bromocriptine): Unveiling the strategy for lactation inhibition - A systematic review of clinical trials

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ABSTRACT

This systematic review aims to evaluate the efficacy and safety of Pyridoxine compared to Dopaminergic agonists (cabergoline and bromocriptine) in post-partum lactation inhibition. Cochrane Central, PubMed/MEDLINE, Cochrane Central, ScienceDirect, ClinicalTrials.gov, Web of Science, CINAHL and Google Scholar, covering the period from inception to November 2023. Additionally, the bibliographies of included articles and previous meta-analyses were screened for any relevant articles. The systematic review was conducted according to the Cochrane Handbook for Systematic Reviews of Interventions. The outcomes of interest encompassed inhibition of lactation, breast pain/tenderness, breast engorgement, milk secretion, fever, mastitis, prolactin level and adverse events related to pyridoxine, cabergoline and bromocriptine. Methodological quality assessment was conducted using the Cochrane risk of bias assessment tool for rigorous evaluation. Three clinical trials assessed the effectiveness of pyridoxine and dopaminergic agents (cabergoline and bromocriptine) for lactation inhibition. It was assessed by using different assessment methods such as a scale for milk secretion, serum prolactin levels, and questionnaires for assessing breast engorgement, breast pain, and milk leakage. On the global assessment of the therapeutic efficacy of dopaminergic agents, it was found that there was significant inhibition of lactation as compared to pyridoxine ($p < 0.001$). In conclusion, this systematic review contributes significant insights into lactation inhibition interventions. Dopaminergic agonists, specifically cabergoline and bromocriptine, stand out as more effective and tolerable choices compared to Pyridoxine. These findings provide a foundation for informed clinical decisions and underscore the need for careful consideration of lactation inhibition strategies in diverse clinical contexts.

Introduction

Lactation is a natural physiological process of producing milk from mammary glands that stands as a cornerstone for the health and well-being of both mothers and infants. However, in some circumstances, the cessation of lactation becomes a necessity, and medical, personal, or societal considerations could drive this decision. Metabolic disorders in infants, such as classic galactosemia, maternal infections like human T-cell lymphotropic virus type I or II, untreated brucellosis, and the use of medications incompatible with breastfeeding, such as chemotherapy, are contraindicated during lactation and hence demand alternative approaches [1–3]. Furthermore, situations like perinatal death or maternal health challenges may also necessitate the inhibition of lactation [4]. A substantial number of women encounter discomfort and milk leakage even after the natural termination of lactation [5]. This necessitates the need for effective interventions addressing both the physiological and psychological aspects of lactation cessation.

In lactation inhibition, approaches range from non-pharmacological methods to pharmacological interventions. Non-pharmacological strategies, including breast binding, tight brassiere usage, infrared lamps, diet restrictions, jasmine flower application, and ice packs, aim to prevent breast engorgement and its associated complications [6]. However,

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the limited and inconclusive data on the efficacy of these methods raise concerns, with up to one-third of women experiencing severe breast pain and reports of increased thromboembolic risks [6].

The landscape of pharmacological interventions for lactation inhibition has evolved, initially involving estrogen and androgen combinations [7]. Despite their effectiveness, concerns about rebound lactation and heightened thrombotic risks limited their usage [7]. A significant breakthrough occurred in 1972 with the introduction of the synthetic dopamine agonist bromocriptine, which proved effective, although challenges such as unpleasant side effects and the need for prolonged administration emerged [8]. Subsequently, in later trials another dopamine agonist cabergoline was also discovered. It's worth noting that the use of dopamine agonists are not recommended in the presence of hypertensive disorders of pregnancy or in women with a history of puerperal psychosis [9,10]. Pyridoxine, a form of vitamin B6, introduces a novel avenue for lactation inhibition, operating as a co-enzyme in the conversion of dopa to dopamine [11]. Although there isn't much available evidence about how well Pyridoxine works, it is still important to conduct thorough research on it to ensure efficient decision making in clinical settings. [12].

In the pharmacological domain, dopamine agonists, specifically cabergoline and bromocriptine, have historically played a role in inhibiting puerperal lactation. While effective, their usage is cautioned in specific conditions mentioned above and variable results have been reported [1–3]. Understanding the comparative efficacy and safety of these dopaminergic agonists to Pyridoxine becomes crucial for informed clinical decision-making This systematic review addresses the current dearth of data on lactation inhibition treatments, focusing on the comparative analysis of Pyridoxine against the dopaminergic agonists; cabergoline and bromocriptine. The objective is to offer a thorough examination of the benefits, risks, and potential limitations associated with each approach. aiming to enhance the precision and effectiveness of lactation inhibition interventions across diverse clinical contexts.

Methods

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [13] and is in alignment with Cochrane collaboration [14]. The study has been registered on PROSPERO (CRD42023486654) on 07/12/2023.

Data sources and search strategy

A thorough search was conducted using the Cochrane Central, PubMed/MEDLINE, Cochrane Central, ScienceDirect, ClinicalTrials.gov, Web of Science, CINAHL (Cumulative Index to Nursing and Allied health Literature) and Google Scholar, covering the period from inception to November 2023. Additionally, the bibliographies of included articles and previous meta-analyses were screened for any relevant articles. The search criteria were not restricted by publication date, language, sample size or other factors. The search terms included relevant PubMed MeSH terms and related text terms, such as pyridoxine, Vitamin B6, bromocriptine, cabergoline, and lactation.

Study selection and eligibility criteria

All identified articles from the systematic search were systematically catalogued in the EndNote reference library, version X8.1 (Clarivate Analytics), with the removal of duplicate entries. The screening protocol entailed the individual scrutiny and selection of studies by two authors, and any disparities were adjudicated by a third author. The inclusion criteria necessitated studies to meet the following specifications: (1) adherence to a randomized or non-randomized controlled trial design involving human subjects; (2) direct comparison of Pyridoxine against Dopaminergic agonists (cabergoline and bromocriptine) in women in the early postpartum period; Studies falling under the categories of observational studies, reviews, conference abstracts, editorials, case reports, and case series were systematically excluded from consideration. Several studies were excluded from the analysis due to missing outcome information, including essential variables such as efficacy in lactation inhibition, occurrences of breast pain/tenderness, breast engorgement, milk secretion, incidents of fever and mastitis, alterations in prolactin levels, and adverse events. As our review aimed to provide a comprehensive analysis of the comparative efficacy and safety of interventions, the absence of crucial outcome data precluded the inclusion of these studies. Despite efforts to consider them for potential inclusion based on available data, their incomplete nature rendered their inclusion impractical and could introduce bias.

Data extraction, quality assessment, and risk of bias

The pertinent information extracted from the incorporated studies encompassed the year of publication, study type, sample size, gender distribution, and baseline characteristics of the subjects, meticulously recorded onto a standardized Microsoft Excel sheet. The primary outcomes under scrutiny included the efficacy in lactation inhibition, occurrences of breast pain/tenderness, breast engorgement, milk secretion, incidents of fever and mastitis, alterations in prolactin levels, and adverse events attributed to the administration of pyridoxine, cabergoline, and bromocriptine. Methodological quality assessment ensued through the application of the Cochrane risk of bias assessment tool [15], and the ROBINS-1 tool [16] facilitated by two independent reviewers, ensuring a rigorous evaluation.

Results

Study selection

A literature search on seven electronic databases retrieved 8147 articles. After the removal of 974 duplicate articles, it yielded 7173 articles. Out of which, 7005 articles were excluded based on title and abstract. Furthermore, 168 full-text articles were assessed for their eligibility out of which 165 articles were excluded as they didn't meet the inclusion criteria. Hence, 2 randomized and 1 non-randomized clinical trials were included in this systematic review. The literature search is summarized in the PRISMA flowchart (Fig. 1).

Study characteristics

There was a total of 3 clinical trials conducted between May 1976 to October 2023. Among these three clinical trials, Boes EG [17] included 97 no breastfeeding mothers who need to inhibit milk production in the postpartum period, Canales ES et al. [18] included 34 puerperal women with contraindications for breastfeeding due to medical reasons, and Schwartz A et Al. [19] conducted in Israel included 88 postpartum patients who did not want to breastfeed.

The sample size ranged from 34 to 97 among which there were a total of 219 postpartum or puerperal women. Out of 219 patients, 107 patients were included in the interventional group and 112 in the control group. The mean age of the patients was 29.707 ± 5.658. The duration of intervention varied in all the three clinical trials ranging from day 1 to day 14. Due to the limited number of studies, meta-analysis could not be conducted.

Various assessment tools were employed to evaluate the outcomes of the studies. One study [17] used rating scales for milk secretion and mammary congestion, while another study [18] used radioimmunoassay. The third study [19] used a questionnaire for assessing breast engorgement, breast pain (for lactation inhibition), and milk leakage on a scale of 0 (no symptom) to 5 (severe symptom) on days 0, 2, 7, and 14. Different outcomes were assessed among which one study [17] evaluated the post-treatment changes in mammary secretion, breast congestion, and therapeutic efficacy of the drug. Two studies [18,19] assessed

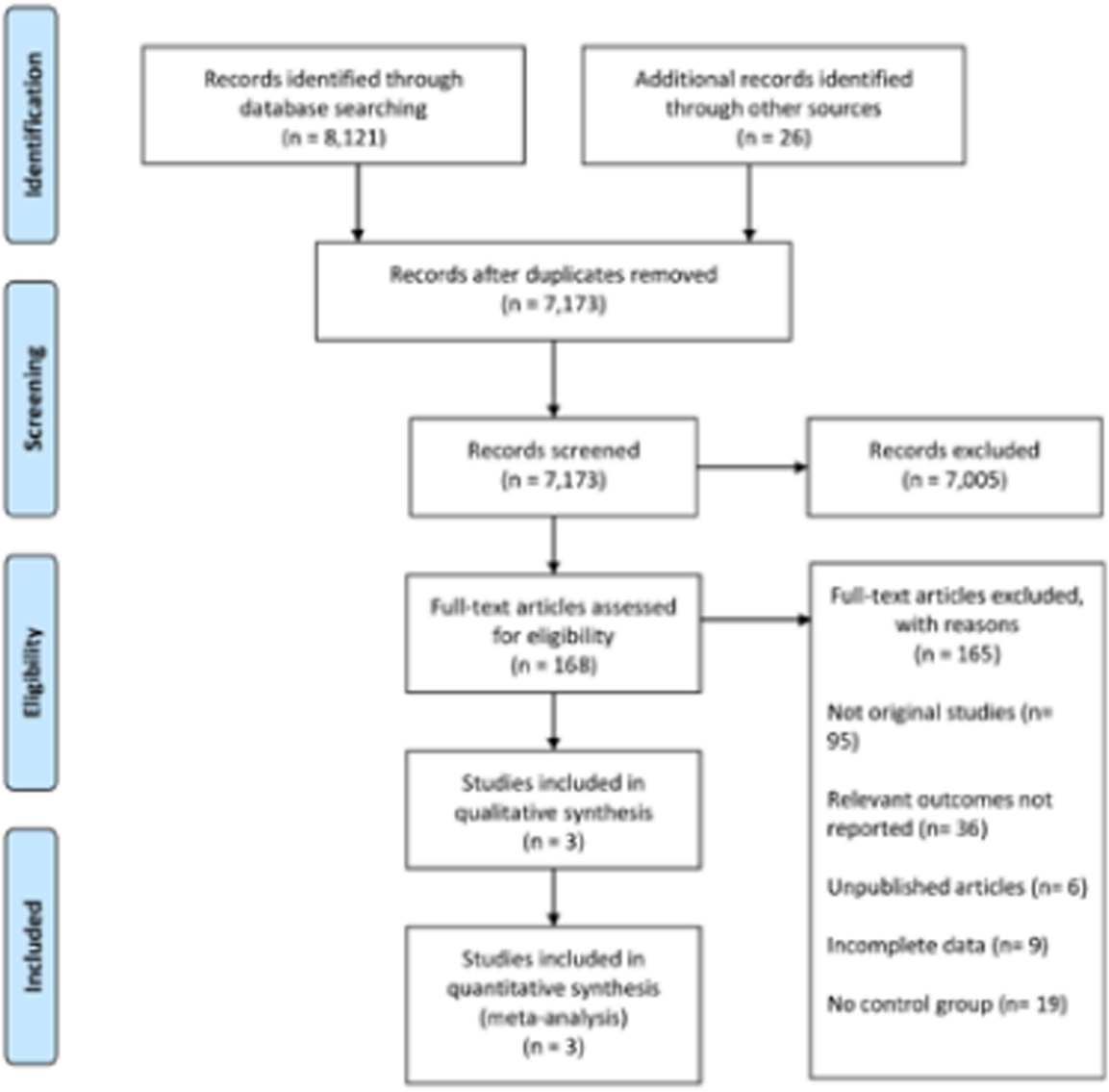

Fig. 1. PRISMA flowchart of the included studies.

breast engorgement. One study [18] assessed serum prolactin levels and lastly, one study [19] evaluated breast pain, the incidence of milk leakage, and adverse effects such as headache, constipation, mastitis, and fever. Detailed characteristics of included studies and population are represented in Table 1.

Risk of bias of included studies

The Cochrane Risk of Bias Assessment tool (RoB 2.0, version 2019) [15] was used to conduct and assess the overall risk of bias in the included studies. The tool used to assess the biases of the trials consists of five domains. If a trial had a high risk of bias in any domain, it was considered to have a high risk of bias overall. On the other hand, if a trial had a low risk of bias or some concerns in any domain, it was considered to have a low risk or some concerns overall. All the studies were analyzed on the intention-to-treat model. One study [17] showed a high risk of bias overall and it was due to no information for bias due to confounding, bias due to the selection of participants, and high risk for bias in the selection of the reported result. Whereas two studies [18,19] showed some concern of bias overall and it was due to some concern of bias in the randomization process and deviations from the intended interventions, respectively. The risk of bias summary and a graph of the included studies are illustrated in Figs. 2-5.

Synthesis of results [17–19]

Effect on mammary secretion and lactation inhibition

In a study conducted by Boes EG [17], the effects of bromocriptine versus pyridoxine were compared for a period of fourteen days. The study found that there were post-treatment changes in mammary secretion. Specifically, there was a significant decrease in secretion in the bromocriptine group (90/159) as compared to the pyridoxine group (14/193) ($p < 0.05$).

Boes EG [17] stated the global assessment of the therapeutic efficacy of bromocriptine vs. pyridoxine on lactation inhibition and found significant inhibition of lactation in the bromocriptine group revealing good efficacy in 142 out of 143 patients as compared to pyridoxine group where 86 out of 136 showed good efficacy ($P < 0.001$). Schwartz A et al. [19] reported the effect of lactation inhibition defined as score 0 for both breast engorgement and pain between cabergoline and pyridoxine, showing a significant decrease in the cabergoline group (29/45) compared to pyridoxine (13/42) at day 2 ($p = 0.001$). At day 7, 35 out of 45 patients in the cabergoline group and 15 out of 43 in the pyridoxine group showed a significant decrease ($p < 0.0001$). There was no

Table 1
The characteristics of included studies and population.

Author (year of study)	Study design	Study Location	Total population (N)	Age (Mean age± SD)	Intervention, Comparator	Case group (n)	Control group (n)	Duration	Tools of assessment	Outcomes
Boes EG (1980)	RCT	NI	97 nonbreastfeeding mothers who need to inhibit milk production in the postpartum period.	NI	Pyridoxine 200 mg 3 times per day for 6 d, with 1 placebo tablet 3 times daily from day 7- 14 bromocriptine 2.5 mg 2 times, with 1 placebo tablet/ daily	48	49	14 days	The rating scales for milk secretion and mammary congestion	Changes in mammary secretion post-treatment: Significantly lower in the bromocriptine group as compared to pyridoxine group ($p<0.05$) Changes in breast congestion post-treatment: significantly decreased in the bromocriptine group as compared to pyridoxine group ($p<0.05$) Global assessment of therapeutic efficacy: Successful inhibition of lactation in bromocriptine group as compared to pyridoxine ($P<0.001$)
Canales ES et al. (1976)	Clinical tral	NI	34 puerperal women with contraindications for breastfeeding due to medical reasons	26 +/- 5.20	Pyridoxine 150 mg/ 3 times daily bromocriptine 7.5 mg daily	14	20	7 days	Serum prolactin levels: Radioimmunoassay	Serum prolactin levels: Women using bromocriptine had a sharp decline in blood prolactin concentrations, although pyridoxine had no influence on this parameter. Breast engorgement: Experienced by all women taking pyridoxine
Schwartz A et al. (2023)	RCT	Afula, Isreal	88 postpartum patients who did not want to breastfeed	31.14 +/- 5.18	Pyridoxine 200 mg/3 times daily cabergoline 1 mg once on postpartum day 1 or divided to 0.25 mg twice a day for 2 days thereafter	45	43	Pyridoxie: 7 days cabergoline: 1 or 2 days	Lactation inhibition and milk leakage: Questionnaire for assessing breast engorgement, breast pain (for lactation inhibition) and milk leakage on a scale of 0 (no symptom) to 5 (severe symptom) on days 0, 2, 7, and 14.	Lactation inhibition defined as a score of 0 for both engorgement and pain: Significantly decreased in cabergoline group when compared to pyridoxine at day2 ($p = 0.001$) and day 7 ($p=<0.0001$). No significant difference between two groups on day 14 ($p = 1$) Mild symptoms defined as a score of 0–2 for both engorgement and pain: significantly lower on day2 ($p = 0.006$), day7($p = 0.01$). No significant difference on day

(*continued on next page*)

Table 1 (*continued*)

Author (year of study)	Study design	Study Location	Total population (N)	Age (Mean age± SD)	Intervention, Comparator	Case group (n)	Control group (n)	Duration	Tools of assessment	Outcomes
										14($p = 1$) Incidence of milk leakage: No significant difference between the two groups at day2 ($p = 0.15$). Significantly lower in cabergoline group on day 7($p = 0.0003$) and day 14 ($p = 0.02$) Number of women reporting adverse effects mainly headache and constipation: Significantly higher in cabergoline group headache($p = 0.01$) and constipation($p = 0.059$) Mastitis and fever: No significant difference between the two groups ($p = 0.67$)

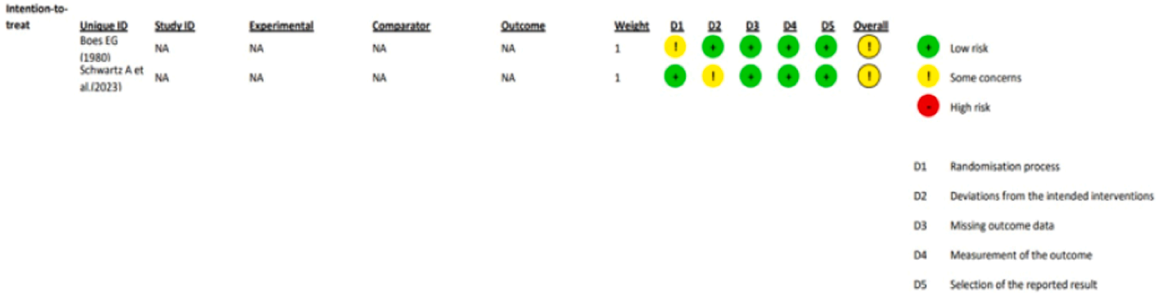

Fig. 2. Risk of bias summary: review authors' judgments for risk of bias for randomized controlled trials.

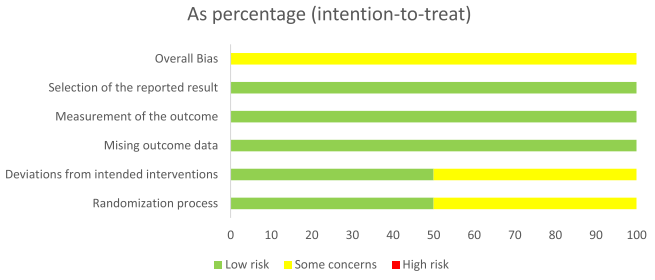

Fig. 3. Risk of bias graph: Review authors' judgments for risk of bias for randomized controlled trials.

significant difference between the two groups (cabergoline group: 40/44 and pyridoxine group: 36/39) on day 14 ($p = 1$). The study also reported the incidence of milk leakage among postpartum women and found no significant difference between the cabergoline (37/45) and pyridoxine group (29/45) at day 2 ($p = 0.15$). There was a significant lowering in the incidence of milk leakage in the cabergoline group (41/45) on day 7 ($p = 0.0003$) and 39 out of 44 patients in the cabergoline group on day 14 ($p = 0.02$), respectively.

Effect on breast congestion and breast engorgement

Boes EG [17] compared the effect of bromocriptine and pyridoxine on post-treatment breast congestion. The study showed a significant reduction in breast congestion in the bromocriptine group (77/109) compared to the pyridoxine group (13/179) ($p < 0.05$).

Canales ES et al. [18] stated that all 14 women who were receiving pyridoxine experienced painful breast engorgement whereas no such effect was observed in bromocriptine. Schwartz A et al. [19] showed that there was a significantly lower incidence of engorgement in the cabergoline group (69 % had no breast engorgement) vs. the pyridoxine group (33 % had no breast engorgement) on day 2 ($p = 0.0009$) and day 7 ($p < 0.0001$) but an insignificant difference on day 14 ($p = 1$). The study also evaluated breast engorgement and pain, which were collectively considered mild symptoms with a score range of 0 to 2. The results showed a significant mild symptom in cabergoline group (36/45) and pyridoxine group (22/42) on day 2 ($p = 0.006$) whereas 40 out of 45 in cabergoline group and 29 out of 43 in pyridoxine group on day 7 ($p = 0.01$), with no significant difference (cabergoline group: 43/44 and pyridoxine group: 38/39) on day 14 ($p = 1$). On day 2, 80 % of the

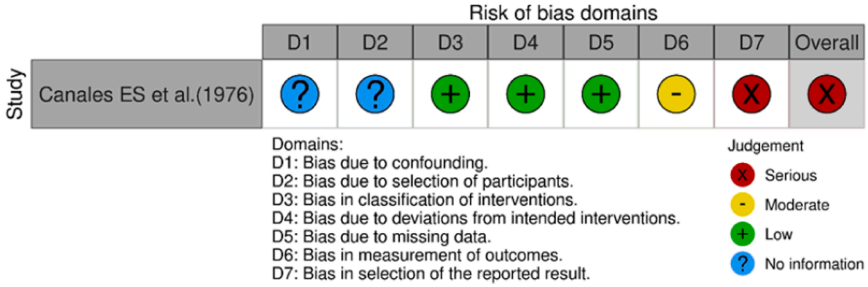

Fig. 4. Risk of bias summary: review authors' judgments for risk of bias for one non-randomized trial.

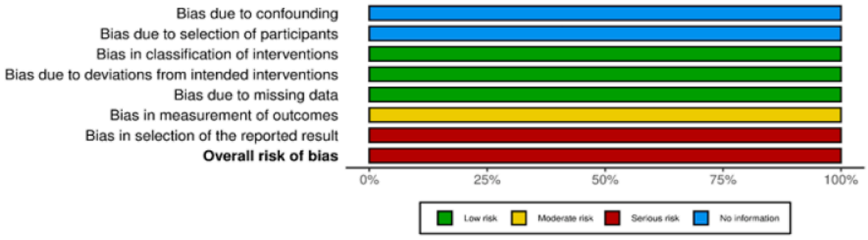

Fig. 5. Risk of bias graph: Review authors' judgments for risk of bias for one non-randomized controlled trial.

cabergoline group and 52 % of the pyridoxine group experienced significant mild symptoms. Schwartz A et al. [19] also evaluated the effect of cabergoline vs. pyridoxine on adverse effects such as breast pain, It significantly reported no complaint of pain in 67 % of patients in cabergoline vs. 40 % in the pyridoxine group on day 2 ($p = 0.01$).

Effect on serum prolactin levels

Canales ES et al. [18] showed the effect of bromocriptine vs. pyridoxine on the serum prolactin levels. It showed that women using bromocriptine sharply declined blood prolactin concentrations, although pyridoxine did not influence this parameter. This study stated that pyridoxine did not affect lactation inhibition along with no effect on prolactin levels.

Effects on adverse effects

Schwartz A et al. [19] also evaluated the effect of cabergoline vs. pyridoxine on adverse effects such as, headache, constipation, mastitis, and fever. It assessed the effect on headaches and found out that 6/45 patients in cabergoline group experienced this adverse effect as compared to pyridoxine group (1/43) ($p = 0.11$). There was also a higher chance of facing constipation in cabergoline (7/45) vs. pyridoxine (1/43) ($p = 0.059$). Lastly, it also reported an effect on mastitis and fever. The rate of mastitis and fever linked to breast engorgement was comparable between the cabergoline (4/45; 9 %) and pyridoxine (2/43; 5 %) groups ($p = 0.67$).

Comment

In our systematic review comparing Pyridoxine with Dopaminergic Agonists (cabergoline and bromocriptine) for lactation inhibition, we observed that Dopaminergic Agonist, bromocriptine is more effective in decreasing mammary secretion, breast congestion, blood prolactin levels, breast engorgement and in inhibiting lactation, as compared to Pyridoxine. Another Dopaminergic Agonist: cabergoline, when compared with Pyridoxine, showed a significantly lower incidence of breast engorgement as well as significant inhibition of lactation. When cabergoline and Pyridoxine are evaluated in terms of adverse effects such as breast pain, headache, constipation, mastitis, and fever, cabergoline was associated with significant increased incidence of breast pain, headaches, and constipation as compared to Pyridoxine, and non-significant increased incidence of fever and mastitis is also reported in cabergoline group.

The existence of a previous Cochrane review which assessed the effectiveness and safety of pharmacological and non-pharmacological interventions for lactation inhibition should be noted. Similar to our review, it also included the randomized trial published by Boes et al. to assess the effectiveness of pharmacological treatments against each other on lactation inhibition. According to this trial, there was no difference in the risk of treatment failure between bromocriptine and pyridoxine for inhibition of postpartum lactation (RR 0.93, 95% CI 0.75 to 1.15) at or less than seven days postpartum. However, in our current systematic review, the authors reported a significant reduction in mammary secretion and breast engorgement with bromocriptine compared with pyridoxine and successful inhibition of lactation in the bromocriptine group compared with pyridoxine. These results are divergent and deserve attention. In contrast to the previously published Cochrane review, our systematic review included two more trials: a non-randomised trial published by Canales in 1976 and a randomised trial published by Schartz last year. There was also insufficient evidence about the side effects of the methods used to suppress breastfeeding in the previously published Cochrane review [20].

Lactation inhibition may be medically necessary in certain situations, such as when a mother is unwilling or unable to breastfeed, when maternal medications may pose a risk to the infant or when there is a risk of transmitting an infectious disease to the infant through breast milk [4]. It is estimated that more than 30 % of mothers in the United Kingdom and the United States do not breastfeed their children, and a higher percentage stop breastfeeding their babies after two weeks of giving birth [21].

There are many non-pharmacological approaches such as breast binding or strapping, emptying of the breast by massage, fluid and diet restrictions and application of external products such as belladonna ointment to the breast and nipples, avoidance of tactile breast stimulation and application of external agents such as cabbage leaves, jasmine flower, and ice packs as well as pharmacological methods to suppress lactation [4]. According to a review by Spitz et al. [6] when these non-pharmacological lactation inhibition techniques are used, up to one-third of women may have significant breast pain throughout the

majority of the first postpartum week.

Among the various pharmacological agents used are Estrogen preparations alone or in combination with Androgen, Pyridoxine and Dopaminergic agonists sch as cabergoline and bromocriptine [7,22–24].

The use of Estrogen preparations alone or in combination are found to be associated with a high rate of rebound lactation and increased risk of thrombosis and pulmonary embolism and are not recommended [25–27]. Bromocriptine's effectiveness in preventing postpartum lactation is widely established but it is also associated with some adverse effects like stroke, convulsions, and psychosis [28–31]. cabergoline is the preferred medication for lactation inhibition. Its effectiveness ranges from 78 % to 100 % [4,32–34]. Nonetheless, cabergoline is not recommended for patients with hypertension, fibrosis, cardiac disease, or hepatic illness [19]. Pyridoxine is also found to have anti lactogenic effect and is used in lactation inhibition [35].

Pyridoxine in the form of pyridoxal phosphate acts as a coenzyme of DOPA decarboxylase, increasing the hypothalamic dopamine level [17]. Dopaminergic agonists such as bromocriptine and cabergoline antagonize prolactin release, which prevents lactogenesis. Dopamine released by the hypothalamus binds to D2 receptors in the anterior pituitary and inhibits prolactin release [19]. Our systematic review focuses on Dopaminergic agonists such as bromocriptine and cabergoline in comparison with Pyridoxine to determine which drug is more efficacious.

Among dopamine agonists, cabergoline is currently the drug of choice for inhibition of lactation. cabergoline's efficacy has been recorded in the literature with multiple doses and results, including lactation inhibition, milk leakage, engorgement, and pain relief [4,32–34]. G Giorda's study reported bromocriptine to have efficacy of 88.9 % in lactation inhibition while efficacy of cabergoline was reported 94.4 % [33].

The efficacy of pyridoxine was also discussed in many studies. Pyridoxine at 200 mg 3 times per day for 6 to 7 days substantially inhibited lactation in approximately 95 % of patients compared with 77 % in the placebo group [11]. Another study reported lactation inhibition in only 17 % in the placebo group [19]. A third study by HN MacDonald et al. reported no significant difference in pyridoxine and placebo groups in terms of lactation inhibition [36]. In one of our double-blind randomized studies [18], bromocriptine was compared with pyridoxine for lactation inhibition. The study included 2 groups of approximately 50 patients each. The Pyridoxine group showed a success rate of 60% vs 100 % success rate of bromocriptine making bromocriptine superior to pyridoxine in terms of efficacy.

A study that examined the role of pyridoxine in reducing serum prolactin for hyperprolactinemia included 60 patients that were divided into 3 groups—placebo, pyridoxine, and cabergoline for 1 month of treatment. Pyridoxine and cabergoline showed significant decrease in prolactin, suggesting pyridoxine's role in lactation inhibition [36]. Another study reported Pyridoxine efficacy in complete lactation inhibition to be 35 % and 28 % after 7 days of treatment [11,37].

A systemic review from 2020 focusing on the safety of cabergoline for lactation inhibition reported adverse events such as dizziness (4.6 %), nausea or vomiting (2.5 %), headache (4.0 %), These adverse events were mild, transient, and self-resolving. No serious adverse event was reported. Single-dose regimens were superior to multidose protocols in terms of safety [38]. Another RCT published in 2022 which compared cabergoline with placebo for lactation inhibition after second-trimester abortion found that the most common adverse effects were constipation, fatigue, headache, and insomnia with a similar rate in both intervention and placebo group [39].

A study on cabergoline reported cabergoline to be better tolerated than bromocriptine, which was previously the standard drug for lactation inhibition. This better tolerability profile of cabergoline is likely the result of a greater affinity for D2 receptors, flat plasma drug concentration, longer plasma half-life, and as well as the shorter duration of therapy compared with bromocriptine This study also reported single dose of cabergoline 1.0 mg was as effective as bromocriptine 2.5 mg twice daily for 14 days. Cabergoline was also found to be associated with a significantly lower incidence of rebound lactation as compared to bromocriptine [39].

Pharmacovigilance studies observing almost 20 years of bromocriptine use for lactation inhibition have revealed rare but serious events [40,41]. Many of the data were collected before the withdrawal of bromocriptine from the market in 1994 [42]. However, a review published in 2015 revealed many serious adverse drug reactions from their pharmacovigilance survey, including neurologic (14.3 %), cardiovascular (70.5 %), and psychiatric (8.6 %) disorders, as well as two deaths. The cardiovascular events primarily consisted of ischemic manifestations ($n = 47$), myocardial infarction ($n = 11$, one death), acute ischemic stroke ($n = 18$, one death), and reversible postpartum cerebral angiopathy ($n = 10$) [40]. A pharmacovigilance study on cabergoline reported twenty-nine serious events. However, the criterion for classification, description of majority of the events, and total number exposed to cabergoline were not listed [43].

Principal findings

The principal findings of our systematic review comparing Pyridoxine with Dopaminergic Agonists (cabergoline and bromocriptine) in lactation inhibition highlight the superior effectiveness of dopaminergic agonists in reducing key parameters such as mammary secretion, breast congestion, lactation, blood prolactin levels, and breast engorgement when compared to Pyridoxine. Notably, cabergoline stands out for its favorable tolerability profile, exhibiting fewer adverse effects like headache, constipation, fever, and mastitis in comparison to Pyridoxine. The review emphasizes the medical necessity of lactation inhibition, influenced by both individual choices and societal trends. It explores the varied efficacy and safety profiles of pharmacological agents, including bromocriptine, cabergoline, and Pyridoxine. These findings contribute valuable insights for clinicians, shedding light on the comparative effectiveness and safety of lactation inhibition interventions and informing evidence-based decision-making in diverse clinical scenarios.

Comparison with existing literature

In comparing our systematic review findings with existing literature, it becomes evident that lactation inhibition is a complex medical necessity influenced by both individual maternal decisions and broader societal trends. Non-pharmacological approaches, such as breast binding and dietary restrictions, pose challenges, with up to one-third of women experiencing significant breast pain during the first postpartum week. Among pharmacological agents, Estrogen preparations are associated with rebound lactation and increased thrombotic risks, making them less favorable. Bromocriptine, historically effective, is linked to adverse effects like stroke and psychosis. Cabergoline emerges as the preferred medication for lactation inhibition, with efficacy ranging from 78 % to 100 %, although caution is warranted in certain patient populations. Pyridoxine, acting as a coenzyme in lactation inhibition, exhibits varied efficacy in studies, emphasizing the need for further investigation. The comparison underscores cabergoline's superiority over bromocriptine and Pyridoxine in terms of efficacy, tolerability, and reduced incidence of rebound lactation, aligning with the evolving landscape of recommendations for lactation inhibition. Ongoing pharmacovigilance studies shed light on the serious adverse events associated with long-term bromocriptine use, emphasizing the importance of monitoring safety profiles in lactation inhibition medications. These findings contribute to a comprehensive understanding of lactation inhibition interventions, aiding clinicians in making informed decisions based on the latest evidence.

Strengths and limitations

To the best of our knowledge, this systematic review represents the

first comprehensive assessment of comparison between pyridoxine and dopaminergic agonists for lactation inhibition. It rigorously evaluates the findings from available studies. Our study's strength lies in its extensive search across multiple databases, resulting in a broader and more comprehensive set of results. Furthermore, nearly all of the studies included in our analysis were high-quality clinical trials with a low to medium risk of bias. However, some limitations must be acknowledged. One major limitation of this review is that the studies included mostly consist of small trials. Although these studies provide insights into the effectiveness of different lactation inhibition methods, their short sample sizes limit their generalizability and made detection of rare but potentially significant side effects difficult between intervention groups. Conducting larger randomized controlled trials would be ideal, but the infrequency with which lactation inhibition is desired makes it challenging. The reliance on primarily poor- to fair-quality studies also raises concerns about the overall reliability of the findings.

Moreover, the included studies exhibit considerable variations in dosages, outcome assessments and data collection methods. This heterogeneity limits direct comparison and decreases the overall strength of the review's findings. Using a combination of questionnaires and standardized breast examinations conducted by healthcare professionals could potentially provide a more comprehensive assessment of lactation inhibition efficacy. Most studies reviewed were published several decades ago, raising concerns about their applicability to current clinical standards and practices. The lack of standard definitions for adverse outcomes and various primary and secondary objectives made this systematic review to be too heterogeneous for a compilation as a meta-analysis. Therefore, the pooled data should be interpreted with caution and are meant to be descriptive rather than quantitative. Additionally, most of the participants in this review were healthy, a factor that limits our ability to utilize this information for women with comorbidities who may require lactation inhibition or inhibition for any indications.

Conclusion and implications

In conclusion, our systematic review underscores the superiority of Dopaminergic Agonists, particularly cabergoline and bromocriptine, over Pyridoxine in effectively inhibiting lactation while exhibiting favorable tolerability profiles. The findings contribute valuable insights into the comparative efficacy and safety of these interventions, guiding clinicians in informed decision-making. The review also highlights the medical necessity of lactation inhibition in various scenarios and discusses societal trends influencing this practice. By incorporating diverse outcomes and considering both non-pharmacological and pharmacological approaches, this study provides a comprehensive understanding of lactation inhibition interventions, emphasizing the importance of tailored clinical considerations in diverse patient populations.

Disclosure statement

The authors report no conflict of interest.

PROSPERO registration

This systematic review has been registered with PROSPERO under the registration number (CRD42023486654) on 07/12/2023.

Consent for publication

Not applicable.

Availability of data and materials

The datasets supporting the conclusions of this article are included within the article and its additional file.

Ethics approval and consent to participate

Not applicable.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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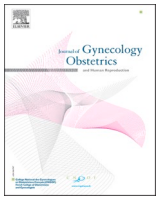

Original Article

Do we want to know the enormity of women's severe menstrual disorders and chronic pelvic pain?

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ABSTRACT

Objective: The purpose of this paper is to call for a nationwide study to assess the prevalence and incidence of women health problems related to menstrual disorders and severe pelvic pain.
Rationale: The exact prevalence and incidence of endometriosis, adenomyosis, severe painful menstrual disorders, and of severe chronic pelvic pain are unknown. These issues severely impact women's quality of life and represent huge costs for our societies. Using adapted questionnaires, recent progresses in diagnosis and increased fundings announced by politicians, we can and should change this situation by performing a nationwide study to assess prevalence and incidence of these women problems in the French general population. The huge, anticipated costs of this study do appear quite reasonable when accounting for the enormous costs and societal consequences of endometriosis, menstrual disorders and severe pelvic pain.
Conclusion: These long-awaited data will improve our understanding of the causes, consequences, and natural history of endometriosis. These data will allow women to better understand that pain is not always related to endometriosis, thus preventing unjustified fears. Physicians will be able to adapt and improve medical managements, particularly the diagnosis. Politicians will have the tools to improve women's health and gender equality.

Endometriosis is thought to affect roughly 10 % (190 millions) of reproductive age women and girls globally [1]. This estimation is probably misleading for many women and frustrating for others. Indeed, severe dysmenorrhea and invalidating dyspareunia are likely much more common than endometriosis. For instance, approximately 25 % of a sample of more than 1000 teenagers were found to have severe dysmenorrhea with pain scores ≥ 7 [2,3] In the same age group, dyspareunia was reported by 21 % of sexually active participants [4]. Hence many patients who complain of severe pain but do not have endometriosis, may feel neglected as years of diagnostic delay is common among endometriosis patients who are still often dismissed by general practitioners and gynecologists by normalization of their symptoms [5,6]. Moreover, severe pelvic pain, with or without associated endometriosis, was reported to be independently associated with a personal history of violence or sexual abuse [7,8] which remains a hushed up but overwhelmingly frequent, up to 30%, drama in 21st century societies [9,10].

To account for the social and economic consequences of these very common women clinical symptoms and diseases, for the difficulties caused by the confusion between severe pain and endometriosis, and for the unknown incidence of endometriosis, the purpose of this call is to suggest that, using recently improved diagnostic tools and increased fundings announced by politician, but yet to be materialized, we can change this situation! Indeed, thanks to the lobbying by the patient advocacy groups and scientists calls for adequate funding [11,12], endometriosis became a national health priority in some countries [13, 14] Hopefully funding for research in endometriosis will increase significantly [15].

This long-awaited change does open up a flood gate of new opportunities. It could be the time to propose new strategies and reevaluate certain commonly accepted or prevailing theories and hypothesis [16] and to assess the magnitude of the incidence and the consequences of dysmenorrhea as well as dyspareunia which may be primary (i.e. with no definitive cause) or secondary (i.e. associated with various pathologies). Many researchers interested in endometriosis once dreamt, of an ethically impossible study, of performing a diagnostic laparoscopy in a large group of randomly selected women in order to ascertain the true incidence of endometriosis in the general population. Nowadays, imaging techniques are increasingly capable of detecting the disease when performed by trained ultrasonographists and or radiologists [17]. These tools significantly changed the landscape of diagnosis and management

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of endometriosis, even though, imaging diagnosis should be used cautiously since an overall false positive rate of 10 % for all endometriosis cases and of 21 % for deep lesions were reported for MRI [18,19]. Similarly, the diagnostic accuracy or expert transvaginal ultrasound in the diagnosis of deep endometriosis depends on the localization of the lesion with a specificity close to 90 % for rectal lesions and to mere 75 % for uterosacral lesions [20]. Other diagnostic approaches such as smartphones applications [21] and biomarkers [22,23] have been developed recently with impressing results [22] which yet have to be validated independently and should until then be used cautiously in clinical practice [24]. Nevertheless, a combination of all these tools may and will likely further diminish the diagnostic value of laparoscopy which still has the advantage to confirm or exclude the disease in patients whose preoperative imaging was inconclusive [25].

Uterine adenomyosis, another possible cause of severe pain, remains the major limit of the surgical diagnosis. Imaging techniques have dramatically transformed the diagnosis of adenomyosis [26]. However, these progresses also illustrate how cautious we should be when using new imaging criteria to diagnose a disease. Indeed, the signs and features for diagnosing adenomyosis as recommended by the Morphological Uterus Sonographic Assessment group became more stringent and restrictive with increasing experience [27,28]. Similarly, experts recently stressed that there is an urgent need for a unified MRI reporting system incorporating standardized terminology to improve the current gaps in knowledge about adenomyosis [29]

Whatever their limits, we do have today powerful tools to diagnose endometriosis and/or adenomyosis in their moderate and severe forms and to rise a high degree of suspicion in many other women who complain of severe pain, deserve a specific care, and may have minimal or mild endometriosis or adenomyosis. Politicians and the public began to recognize that severe menstrual pain and associated diseases are very common and can severely impact on women's lives. Last year Spain became the first European country to entitle workers to paid menstrual leave which will be covered by the government [30]. Although a similar project was recently rejected by the French senate [31], endometriosis is nonetheless recognized as a national health priority in France [13] and the French Health Ministry should agree to fund or help to fund, organize, and run a prospective national study to assess the magnitude of these problems in France. The world is waiting for the launch of such study which appears critical to help to improve the health of at least 30 % of women.

For different age groups, a statistically representative group of women would be randomly selected from the national security system database. This group would be contacted and assessed using validated questionnaires for quality of life [32,33], post-traumatic stress disorders [34,35], pain severity scales [36] and smart phones applications [31]. Medical, surgical and obstetrical personal history would also be collected. Personal history of familial or sexual violence, would be assessed for the following reasons. Preliminary studies suggested that trauma to the vaginal cul de sac associated with an hemoperitoneum could precede a deep endometriotic nodule [37]. The peritoneum may be traumatized indirectly without entering the peritoneal cavity as veterinarian showed that transrectal ovarian palpation in bovine induced peritoneal damages [38]. Third, it is estimated that approximately 10 % of french [39] and 20 % of english and welsh adults have a personal history of childhood maltreatment or violence [40]. These personal histories are more common in women than in men, and significantly more common in women who complained of severe pelvic pain irrespective of the presence of endometriosis [7]. So, it is sensible to assess these issues when attempting to ascertain the magnitude of the consequences of severe gynecological pain and menstrual disorders.

Then every woman would be referred to trained ultrasonographists and radiologists for a vaginal ultrasound and an MRI performed according to a preestablished protocol [41] and interpreted independently by two expert radiologists. Patients with negative imaging results would be assessed using one or two biomarkers [22,42]. Blood and saliva samples would be stored and or assessed based on the money available for the study [43].

The cost of this study appears as prohibitive. If including 10 000 women and spending 1000 € for each, 10 000 000 € would be necessary. However, this initial impression should be carefully evaluated accounting for the following points. (a) The costs of endometriosis [44], mainly attributable to productivity costs, are very high similar to that of diabetes, Crohn disease and polyarthritis and were estimated to be close to 10 000€/year, more than 10 years ago [44]. So, the cost of the study would be equivalent to the cost of treating 1000 patients for one year. (b) The cost of abnormal menstruation and or pain, often wrongly attributed to endometriosis are probably higher as at least the 30 % of women are affected by these severe symptoms associated with a significant loss of productivity and an ever-increasing number of clinical consultations, pelvic ultrasonographic examinations and MRIs. (c) The cost of the treatment of endometriosis and of possibly endometriosis related menstrual disorders are going to increase significantly for several reasons. [1] New drugs, more expensive than older ones are entering the market [45,46]. (2) More sophisticated and expensive surgical tools are increasingly being used [47,48]. (3) Fertility preserving procedures are often proposed to, or asked by, young women afraid of the risks of endometriosis related infertility [49,50]. (4) As chronic pain is not always effectively treated by conventional treatments more and more patients are using alternative therapies which are often expensive and only covered by private insurances. [5] The costs of an inadequate diagnosis on a personal life are difficult to evaluate and likely to be underestimated when social media are amplifying the risks and the consequences of any medical problem. Finally, the cost incurred due to childhood and woman violence are huge, between 3.5 and 5.5 billion dollars in Australia and the overall costs of all violence can be even higher [51]. Extrapolating from a sample of studies from countries that had calculated the costs of all forms of violence, the Copenhagen Consensus, under the United Nation Organization authority, estimated that the global cost was US$ 9.5 trillion or 11 % of global Gross Domestic Product (GDP) [51]. In light of these considerations, the estimated costs of this study appear quite reasonable and acceptable.

The benefits of this study would be considerable, knowing the true incidence of endometriosis in our population would avoid unjustified fears, allow adequate managements of the disease and of other menstrual and sexual pain problems. A prevalence of 5, 10 or 30 % does not at all have the same consequences. Having at the same moment, a better evaluation of all the consequences of sexual and children violence will undoubtedly significantly impact the management of these situations. This study could be a tremendous opportunity to independently confirm the very promising results of the salivary test [22], which recently entered the market, particularly to assess its value among asymptomatic patients, as markers results could possibly be influenced by clinical symptoms and complications of the disease. Similarly, a better assessment of the questionable role of MRI in these situations [52] will be possible. Knowing the percentage of asymptomatic endometriosis and or adenomyosis would impact all clinical research, since the definition of a "reasonable" or realistic control group would be much easier. This would also allow us to have a much more accurate knowledge of the consequences of these diseases on fertility, chronic pain and altered quality of life. A much better appreciation of the natural history of the disease would be accessible when comparing the results obtained in different age groups and assessing the clinical history of the woman diagnosed with the disease. Undoubtedly many other significant clinical improvements will appear as many researchers will have access to the results. Politician will know how to adapt their policy to improve women's health problems, being a woman may even change significantly as some words, such as severe dysmenorrhea, would have a real signification rather than an imaginary or a fanciful one. Diagnostic delay will decrease as awareness of the results will likely encourage woman and physicians to accept thesr symptoms as abnormal, or in contrast as being reassured by the normality of what they are facing with.

Therefore, this study should be undertaken now, to identify the magnitude of these problems so as to optimize our health policy and to be able to offer a better quality of life to many women and thus finally use the tools required to improve gender equality in our societies! It is beyond the scope of this call to elaborate the entire protocol. An expert group should be organized to elaborate and propose the protocol to the scientific community.

Contribution to authorship

M.C conceived and designed the paper wrote the manuscript and approved the final version to be submitted.

Declaration of competing interest

The author has no conflict of interest to declare.

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