Review Article

Does Cabergoline Prevent Ovarian Hyperstimulation Syndrome? Systematic Review

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ABSTRACT

The main objective of this study is to evaluate the available evidence on the efficacy of cabergoline in the prevention of ovarian hyperstimulation syndrome (OHSS) in patients undergoing fertility treatments. A comprehensive search of four databases identified 712 relevant publications. After duplicate removal using Rayyan QCRI and relevance screening, the search identified 346 publications, of which 101 full-text articles were reviewed, six of which met the eligibility criteria for the evidence synthesis. We included six studies with a total of 919 women: 440 in the cabergoline group and 479 in the control group. The prevalence of OHSS in the cabergoline group ranged from 8.3% to 65.6%, for an overall prevalence of 34.8%. In the control group, the incidence of OHSS ranged from 10.59% to 77.8%, for an overall prevalence of 32.9%. Cabergoline is effective in reducing moderate to severe OHSS, especially compared to placebo, making it a suitable choice for high-risk women. However, it is less effective than calcium gluconate in preventing mild OHSS, and the incidence of mild cases is higher. Alternative treatments, including quinagolide, diosmin, and calcium injections, have shown superior efficacy in preventing OHSS. In conclusion, cabergoline effectively reduces moderate to severe OHSS, especially compared to placebo, but is less effective than calcium gluconate in mild cases. Alternative treatments, such as diosmin, diosmin, and calcium injections, may offer better outcomes in specific cases. Tailoring treatment based on the patient's risk factors is essential.

Keyword: Cabergoline; OHSS prevention; Calcium gluconate; Alternative treatments; Reproductive medicine; Systematic review.

Introduction

OHSS is a severe and sometimes fatal side effect of assisted reproductive technologies (ART), especially for women having controlled ovarian stimulation (COS) and in vitro fertilization (IVF) [1].

OHSS is characterized by the excessive response of ovaries to hormonal stimulation, leading to enlarged ovaries, abdominal distension, and fluid accumulation in the abdominal cavity.

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In severe cases, OHSS can result in respiratory distress, kidney failure, thromboembolic events, and even death. Given the growing prevalence of ART and the associated risks with OHSS, there is an increasing interest in effective preventive measures. Among these, Cabergoline has emerged as a promising candidate [2]. OHSS primarily arises due to the overstimulation of the ovaries, often induced by exogenous gonadotropins used to promote follicular development. Human chorionic gonadotropin (hCG) and other hormones are used to induce ovulation and egg retrieval during a normal IVF cycle [3]. A series of biochemical processes might result from an overabundance of the ovarian response in certain women. Increased vascular permeability brought on by high concentrations of vasoactive substances, most notably vascular endothelial growth factor (VEGF), is the disease. As a result, fluid leaks into the peritoneal cavity, exacerbating the disease and leading to ascites [2]. Risk factors for OHSS include polycystic ovary syndrome (PCOS), younger age, high basal estradiol levels, and a high number of developing follicles. Women who present with these characteristics during stimulation are at an elevated risk for developing OHSS. Recognition of these risk factors has led clinicians to adopt strategies aimed at minimizing the occurrence of this syndrome [4]. Cabergoline is a dopamine agonist primarily used in the treatment of disorders related to hyperprolactinemia, such as prolactinomas. However, its application has extended into reproductive medicine, especially when it comes to OHSS prevention [5]. By activating dopamine receptors, the drug prevents excessive gonadotropin-releasing hormone (GnRH) secretion, which in turn lowers the pituitary gland's production of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) [6]. The utility of Cabergoline in OHSS prevention arises from its ability to modulate ovarian function. Cabergoline lowers the risk of OHSS by inhibiting gonadotropin activity. Numerous studies have shown that administering cabergoline during the stimulation phase can significantly reduce the incidence of OHSS, especially in high-risk women [7]. A number of meta-analyses and randomized controlled trials have attempted to assess how well cabergoline works to lower the frequency and severity of OHSS [3, 8]. In a noteworthy research, cabergoline was given to IVF patients throughout the luteal phase in addition to their regular fertility drugs. Comparing the medication-treated group to a control group, the results showed a significant decrease in OHSS instances. Additionally, although maintaining similar pregnancy rates, individuals in the cabergoline group had a decreased incidence of moderate to severe OHSS [8]. Another meta-analysis encompassing a range of studies reinforced these findings, concluding that the use of Cabergoline resulted in a significant reduction in OHSS incidence [9]. This evidence points to the dual benefit of Cabergoline, not only in preventing the clinical manifestation of OHSS but also in maintaining the efficacy of IVF treatments. Potential underlying mechanisms proposed include the modulation of ovarian response and adjustments in ovarian vascularity and permeability, both of which contribute to the risk dynamics of OHSS [9]. As evidence supporting the use of Cabergoline for OHSS prevention continues to accumulate, its integration into clinical practice requires careful consideration. Healthcare providers involved in ART are encouraged to assess patients' individual risk profiles prior to initiating gonadotropin therapy. For those identified as high-risk patients, the introduction of Cabergoline can be an essential aspect of a comprehensive prevention strategy [10, 11]. OHSS is a serious complication associated with ovulation induction protocols, particularly in ART. Given the rising prevalence of infertility treatments, understanding interventions that may prevent OHSS is of paramount importance. Cabergoline, a dopamine agonist traditionally used for conditions such as hyperprolactinemia, has garnered attention for its potential role in mitigating OHSS. Despite advancements in reproductive medicine, OHSS remains a significant clinical challenge, with no universally accepted preventive strategy. Incidences of mild to severe OHSS vary greatly, complicating treatment protocols. Current interventions show mixed efficacy, and the potential of Cabergoline as a preventative measure is inadequately explored in existing literature. In order to give a thorough grasp of the potential use of Cabergoline as a preventative therapy against OHSS, this review attempts to assess the data currently available about the drug's efficacy in preventing OHSS in patients receiving reproductive therapies.

Methods

To maintain openness and scientific rigor, this systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards. This review's main goal was to assess Cabergoline's effectiveness in avoiding OHSS. To find pertinent English-language papers, a thorough search technique was used across many electronic databases, including PubMed, Web of Science, SCOPUS, and Science Direct. To focus the search,

terms including "cabergoline," "ovarian hyperstimulation syndrome," "OHSS prevention," and "assisted reproductive technology" were employed. After screening the search results, two independent reviewers chose studies that fit the qualifying requirements, retrieved the data, and evaluated the included studies' quality.

Eligibility Criteria

Inclusion Criteria:

• Research on Cabergoline's potential to prevent OHSS in individuals receiving ovarian stimulation for ART.

• Studies reporting outcomes such as incidence of OHSS, severity of OHSS, and pregnancy rates.

• Only peer-reviewed articles published in English within the last 10 years were included to ensure the relevance and timeliness of the evidence.

• Cohort studies, case-control studies, and randomized controlled trials (RCTs) were among the study types that were thought to offer a thorough examination.

Exclusion Criteria:

• Research that doesn't particularly discuss how Cabergoline can help avoid OHSS.

• Research focusing solely on other interventions for OHSS prevention without comparison to Cabergoline.

• Studies involving animal models, in vitro experiments, or theoretical analyses.

• Non-peer-reviewed literature, such as conference abstracts, editorials, or commentaries.

• Studies with insufficient data on OHSS outcomes or those conducted in non-clinical settings.

Data Extraction:

The Rayyan (QCRI) tool was used to manage and screen the search results, ensuring consistency and reliability. The inclusion and exclusion criteria were used to assess abstracts and titles for relevancy. Two reviewers separately examined full-text papers of possibly qualifying research. Discussion and agreement were used to settle any differences in the choice of studies. Key information was gathered using a standardized data extraction form, which included:

• Title, authors, and year of publication of the study.

• Examine the layout and setting.

• Participant demographics (e.g., age).

• Intervention details (e.g., Cabergoline dosage).

• Any reported adverse effects of Cabergoline.

Data Synthesis Strategy: The extracted data were synthesized qualitatively and presented in summary tables to facilitate comparison across studies. Key findings related to the efficacy of Cabergoline in preventing OHSS, including its impact on OHSS incidence, severity, and pregnancy outcomes, were summarized. If sufficient homogeneous data were available, a meta-analysis was conducted using appropriate statistical methods to pool effect sizes and assess heterogeneity. Subgroup analyses were performed based on factors such as Cabergoline dosage, patient characteristics, and study design.

Quality review: The selected RCTs were critically evaluated using the Cochrane Risk of Bias Instrument [12]. This test assesses the risk of bias in seven areas: the creation of random sequences, the confidentiality of allocation, participant and employee blinding, result evaluation blinding, insufficient outcome data, selective reporting, and other sources of bias. Each of these categories had a risk of bias that was categorized as low, uncertain, or high.

Results

Using the given search technique, 712 papers were found (Figure 1). Following the elimination of duplicates (n = 366), 346 articles were assessed using the abstract and title. Of these, 301 did not meet the requirements for eligibility; therefore only 45 full-text articles were left for a thorough examination. Six individuals met the criteria for eligibility with synthesised evidence for analysis. Clinical results and sociodemographics. There were 919 women in all across 6 investigations, with 440 in the Cabergoline group and 479 in the control group. Four studies were RCTs [14, 16-18] and two were case-controls [13, 15]. Two studies were implemented in Turkey [14, 15], two in Egypt [17, 18], one in Japan [13], and one in Iran [16]. The prevalence of OHSS among patients who received cabergoline ranged from 8.3% [14] to 65.6% [13], with a total prevalence of 153 (34.8%). The incidence of OHSS among patients in the control group ranged from 10.59% [15] to 77.8% [13], with a total prevalence of 158 (32.9%). Among the included studies, three supported cabergoline as an effective intervention for preventing moderate to severe OHSS compared to placebo or calcium gluconate [13, 14, 15]. However, two studies indicated that alternative treatments, such as quinagolide and diosmin, were more effective than cabergoline in reducing OHSS incidence [16, 18]. According to a different trial, calcium infusion reduced the overall incidence and severity of OHSS while preserving comparable pregnancy outcomes better than cabergoline [17]. Cabergoline effectively reduces moderate to severe OHSS, particularly compared to placebo, making it a viable prophylactic option in high-risk women [13, 14]. However, it is less effective than calcium gluconate in preventing mild OHSS and is associated with a higher incidence of moderate cases [15].

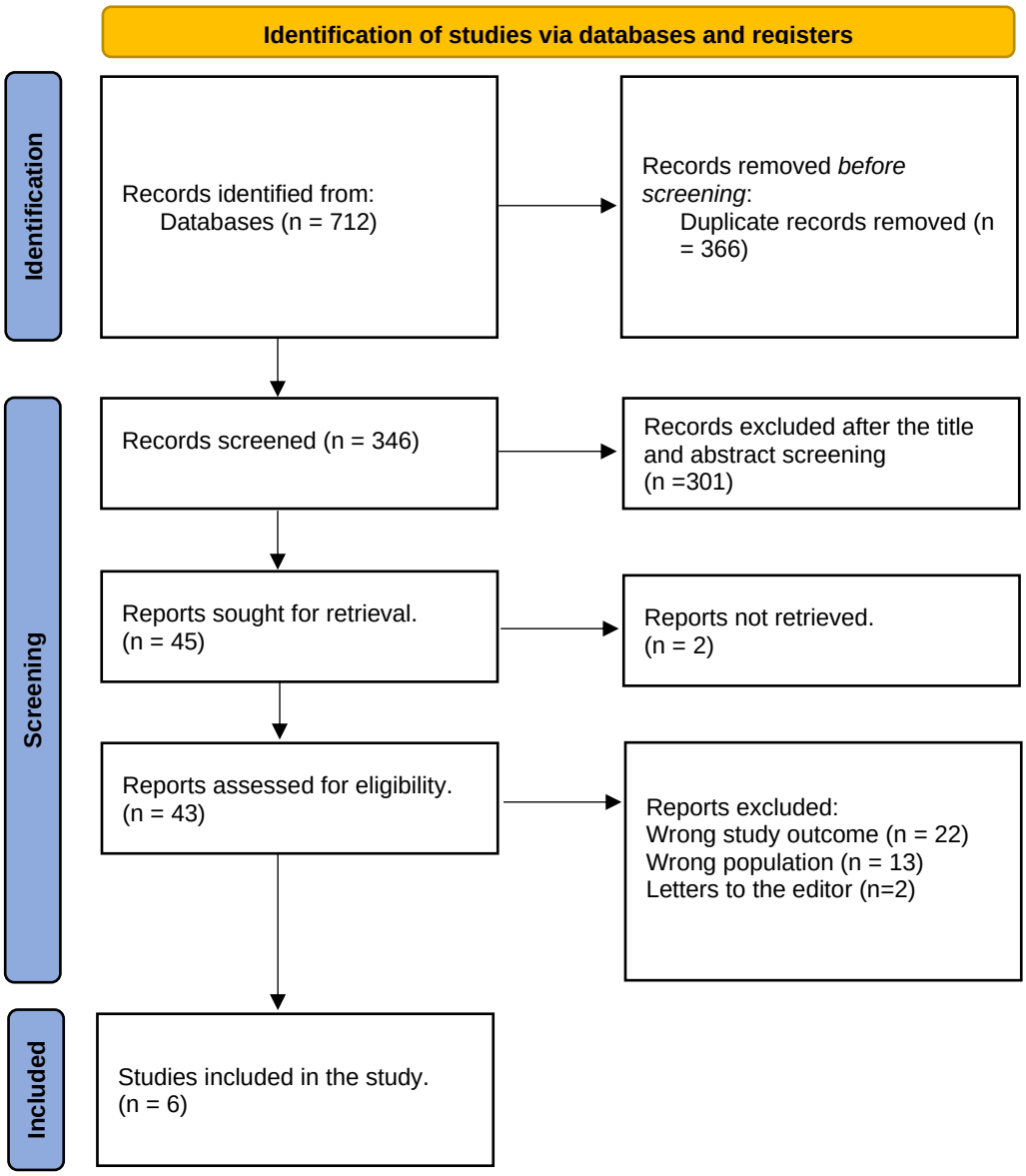

Figure 1: PRISMA flowchart.

Table 1: Outcome measures of the included studies.

Study ID	Study design	Country	Sociodemographic	Comparator	OHSS in Cabergoline (%)	OHSS in controls (%)	Intervention dosage	Main outcomes
Inoue et al., 2015 [13]	Case-control	Japan	Cases: 41 Controls: 82 Mean age: 35.1	Placebo	40 (65.6 %)	98 (77.8 %)	0.5 mg after oocyte retrieval	Cabergoline has a positive impact on preventing moderate to severe ovarian volume reduction-related OHSS.
Kilic et al., 2015 [14]	RCT	Turkey	Cases: 36 Controls: 34 Mean age: 31.7	Placebo	3 (8.3%)	7 (20.5 %)	0.5 mg daily for 8 days	When administered by women who are at high risk for OHSS during controlled ovarian stimulation, cabergoline lowers the occurrence of that complication.
Turktekin et al., 2022 [15]	Case-control	Turkey	Cases: 85 Controls: 85 Mean age: 27.9	Calcium gluconate	7 (8.24%)	9 (10.59 %)	0.5 mg daily for 8 days	Cabergoline effectively prevents severe OHSS, whereas calcium gluconate shows a higher occurrence of mild OHSS. However, moderate OHSS is more common with cabergoline.
Taheripanah et al., 2018 [16]	RCT	Iran	Cases: 63 Controls: 63 Mean age: 31.2	Quinagolide	30 (47.6%)	14 (22.2 %)	0.5 mg cabergoline daily for 7 days	Among patients with elevated risk undergoing ICSI, quinagolide was more successful than cabergoline in preventing OHSS.
Elnory & Elmantwe, 2018 [17]	RCT	Egypt	Cases: 115 Controls: 115 Mean age: 29.2	Calcium gluconate	32(27.8 %)	16 (13.9 %)	0.5 mg/day taken orally for 7 days	With similar pregnancy outcomes, calcium infusion reduces the overall incidence and severity of OHSS more effectively than oral cabergoline intake from ovum pick up day.
Saad & Mohamme	RCT	Egypt	Cases: 100 Controls: 100	Diosmin	41 (41%)	14 (14%)	0.5 mg daily for 8 days	When administered to high-risk individuals, diosmin was more successful than cabergoline in

d, 2017 [18]			Mean age: 29.1					preventing severe OHSS and lowering OHSS occurrence rates.

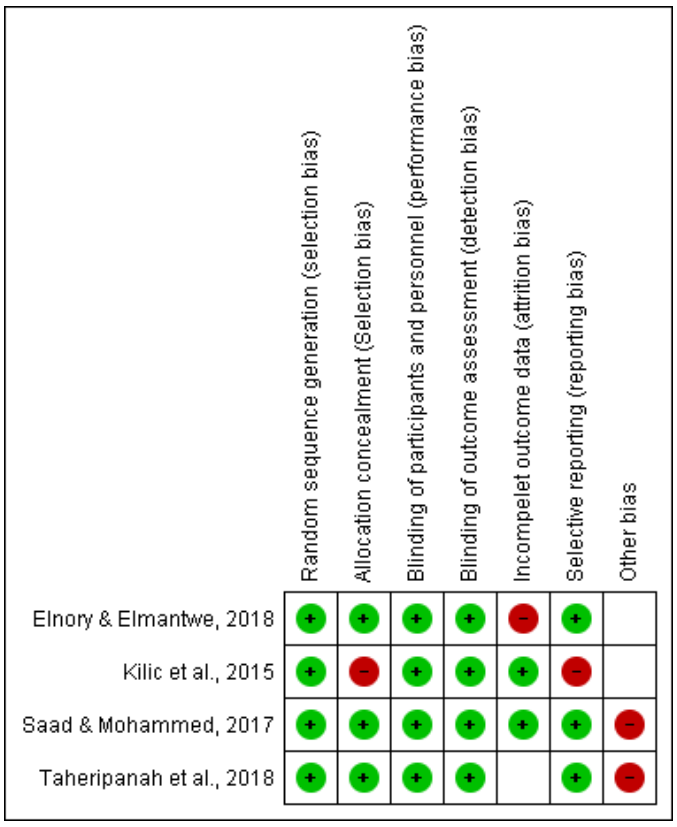

Figure 1: Risk of bias assessment for included studies.

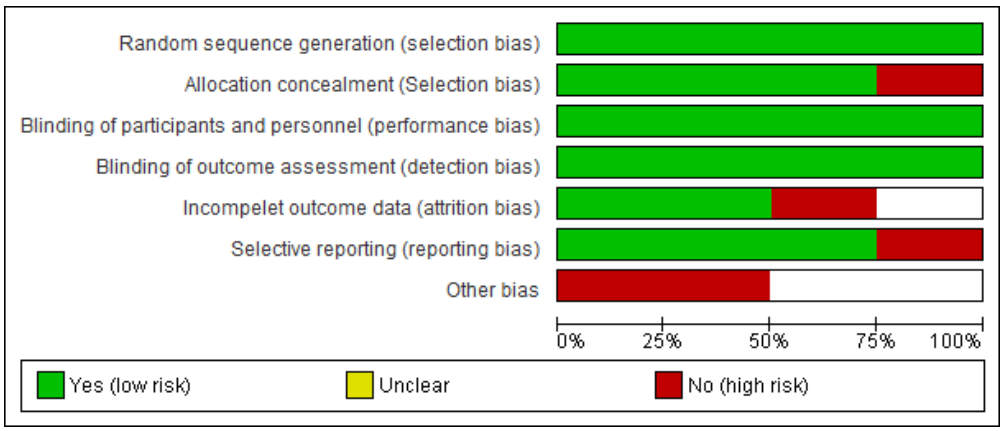

Figure 2: Cochrane risk of bias assessment.

Comparisons with other treatments indicate that quinagolide, diosmin, and calcium infusion provide better OHSS prevention, suggesting that alternative interventions may offer superior outcomes [16, 17, 18].

Discussion

This analysis highlights the role of cabergoline in reducing moderate to severe OHSS, particularly when compared to placebo. The findings suggest that cabergoline can be a viable prophylactic option for high-risk women undergoing controlled ovarian stimulation. However, its efficacy varies depending on the comparator. It performs less well versus calcium gluconate because it is linked to a greater incidence of mild OHSS, even if it is more effective than a placebo. Additionally, alternative treatments such as quinagolide, diosmin, and calcium infusion demonstrated superior outcomes in OHSS prevention. These variations in efficacy indicate that treatment choice should be tailored based on patient risk factors and response to therapy. However, this study highlighted that among women undergoing COS who are more vulnerable to this consequence, cabergoline reduces the incidence of OHSS. However, Leitao et al. emphasized that Cabergoline lowers the risk of OHSS in women undergoing COS who are highly susceptible to this complication [20]. Guo et al. reported that when compared to placebo or blank control groups, cabergoline significantly lowers the incidence of moderate to severe OHSS, according to the network meta-analysis. It also has a 22% chance of being the most effective preventive medication out of the five successful medical treatments mentioned above. Although both calcium and cabergoline notably target the VEGF pathway, their preventive mechanisms differ slightly: calcium works by lowering the level of VEGF, while cabergoline blocks the VEGF-stimulating VEGFR-2. Although calcium is given intravenously and cabergoline is more costly, both therapies are suitable in terms of their ability to prevent OHSS and their safety during pregnancy [21]. Theoretically, the dopamine agonist cabergoline can prevent the VEGFR-2 receptor from becoming phosphorylated, which would lessen vascular leakage into the third compartment and ease different OHSS presentations following the COS cycle [21]. Another meta-analysis by Baradwan et al. [23] discovered that calcium infusion may be a more effective way to reduce the occurrence of severe OHSS than cabergoline. A recent network meta-analysis found that the chemical drugs that prevented OHSS the most effectively were calcium, hydroxyethyl starch, and cabergoline, in decreasing order [23]. Only three trials comparing calcium infusion to cabergoline were included in the same network meta-analysis [23, 24].

Cabergoline remains a widely used intervention for OHSS prevention, particularly for reducing moderate to severe cases. But given its relative efficacy, doctors must to carefully weigh their alternatives, particularly for patients who are at a high risk of developing severe OHSS. Calcium gluconate may be preferable for preventing mild OHSS, while diosmin and quinagolide could offer better protection in certain populations. These findings support the need for individualized treatment approaches in ART to optimize patient outcomes.

Strengths: This analysis draws from multiple studies across different populations, providing a comprehensive evaluation of cabergoline's effectiveness. The findings are more reliable when randomized controlled trials and case-control studies are included. Furthermore, the comparison with multiple alternative interventions allows for a broader understanding of cabergoline's place in OHSS prevention strategies.

Limitations: Variability in study design, dosage regimens, and patient populations may influence the comparability of findings. Small sample numbers in several research may have the affected statistical power. Inconsistencies in prevalence rates may also be caused by variations in OHSS diagnostic standards and reporting practices. To validate these results and improve therapy recommendations, further extensive, standardized studies are required.

Conclusion

Cabergoline is effective in reducing moderate to severe OHSS, particularly compared to placebo, but it may be less effective than calcium gluconate for preventing mild OHSS. Alternative treatments such as diosmin, quinagolide, and calcium infusion have shown superior efficacy in certain cases, suggesting that treatment choice should be tailored based on patient risk factors. Future research should focus on optimizing prevention strategies and identifying the most suitable interventions for different patient profiles.

Conflict of Interest

None

Funding

None

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