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REVIEW ARTICLE OPEN ACCESS

Cabergoline Use and Pregnancy Outcomes: A Systematic Review

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Received: 9 December 2024 | **Revised:** 25 February 2025 | **Accepted:** 8 March 2025

Funding: The authors received no specific funding for this work.

Keywords: cabergoline | congenital abnormalities | dopamine agonists | ovarian hyperstimulation syndrome | prolactinoma | spontaneous abortion

ABSTRACT

Introduction: Lack of available expert guidelines leads clinicians to interrupt cabergoline treatment upon confirmation of pregnancy and consider switching to bromocriptine, which is more commonly used during pregnancy but is poorly tolerated.

Objective: The objective of this review was to evaluate pregnancy outcomes, primarily major malformations and spontaneous abortions, after pregnancy exposure to cabergoline during the first trimester compared to pregnancy exposure to other comparators or no treatment.

Methods: An Embase, Pubmed, Google Scholar, and ClinicalTrials.gov search was performed. Full articles published before October 27, 2022, and evaluating the effect of cabergoline on major malformations and spontaneous abortions were considered for inclusion in the review. Search results were manually screened and selected by two independent reviewers.

Results: Totally, 2186 records were identified. After removal of duplicates and screening of abstracts, 65 full-text articles were consulted. Thirty articles corresponded to our selection criteria and were included in the systematic review. This review identified 1662 pregnancies exposed to cabergoline. Most studies did not find an increased risk of congenital malformations or spontaneous abortions with cabergoline compared to other comparators or no treatment. Overall study quality was low, and there was high heterogeneity between studies.

Conclusion: This review revealed no negative impact on major malformations and spontaneous abortions of cabergoline use in pregnancy compared to other comparators or no treatment. However, additional high-quality studies are needed to further study the safety of cabergoline use during pregnancy.

Trial Registration: PROSPERO, CRD42021256219 (October 19, 2021)

1 | Introduction

Cabergoline is a long-lasting dopamine (DA) agonist. It is the gold standard drug to treat hyperprolactinemia and prolactinoma (Glezer and Bronstein 2014) by inhibiting prolactin secretion from lactotroph cells of the pituitary gland. It can also be used to prevent and to treat ovarian hyperstimulation syndrome (OHSS) by reducing vascular permeability (Bassiouny et al. 2018). However, there is a lack of evidence on the safety of this medication in pregnancy. In current clinical practice,

clinicians typically discontinue cabergoline when pregnancy is discovered in their patients.

Bromocriptine is another DA agonist that has been used for a longer period than cabergoline for acromegaly, hyperprolactinemia, and prolactinoma, but it is not indicated for OHSS (Huang et al. 2018). Its safety during pregnancy is well documented (Krupp and Monka 1987). On the other hand, evidence suggests that cabergoline is associated with fewer adverse effects than bromocriptine, greater efficacy in hyperprolactinemic patients, and longer-lasting benefits after treatment discontinuation compared to bromocriptine (Ferrari et al. 1992; Rains et al. 1995). Furthermore, due to its long-lasting effect (elimination half-life 63–69 h [Product Monograph 2016] for cabergoline versus 4.5–6 h [Micromedex Product Information 2019] for bromocriptine), cabergoline can be taken once a week, whereas bromocriptine requires daily administration. This prolonged effect may raise concerns among clinicians, as patients of reproductive age may inadvertently expose their embryo to the drug for an extended period if they become pregnant, especially given the lack of safety data on cabergoline during pregnancy.

The objective of this study is to conduct a systematic review comparing the incidence of pregnancy outcomes, mainly major malformations and spontaneous abortions, in patients on cabergoline therapy during the first trimester of pregnancy compared to those receiving other treatments or no treatment.

2 | Materials and Methods

This study was registered with PROSPERO (ID: CRD42021256219). An Embase, PubMed, and Google Scholar search was performed using both free text and Mesh terms covering the following concepts: cabergoline, indication for cabergoline, pregnancy outcomes, neonatal outcomes, and developmental outcomes. A research strategy was elaborated using terms to cover these concepts, such as cabergoline, pregnancy, hyperprolactinemia, prolactinoma, and OHSS (Supporting Information—Search strategy). Full articles published before October 27, 2022, and written in English or French were considered for inclusion in the systematic review. A search in ClinicalTrials.gov was also performed. We reviewed studies evaluating the impact of cabergoline on the incidence of pregnancy and obstetric outcomes, as well as neonatal, fetal, embryonic, and developmental outcomes. Initially, we wanted to include all articles reporting at least one of these outcomes. During our literature review, we decided to include only the studies evaluating specifically major malformations, spontaneous abortions, or both outcomes because other outcomes were rarely studied, and most of them were evaluated as secondary outcomes. All studies reporting at least one of these outcomes with exposure to cabergoline during the first trimester of pregnancy or within the 2 weeks preceding conception, regardless of concomitant disease or pathology, were reviewed. We selected this exposure window because the first trimester is the critical period for major malformations and spontaneous abortions. Additionally, due to the long half-life of cabergoline, patients may still be exposed to the drug during the early stages of the first trimester if the last dose was taken within 2 weeks before conception. Since it takes five half-lives for 97% of the drug to be eliminated after stopping the medication, this window of exposure is relevant.

We included randomized controlled trials, prospective cohort studies, and retrospective cohort studies and excluded meta-analyses, reviews, case series, and case reports. Studies reporting only treatment effectiveness, instead of major malformations or spontaneous abortions, were excluded. Search results were screened (titles, abstracts, full texts) and selected by two independent reviewers (A.-S.O., Z.T.) according to established selection criteria. Disagreements were resolved by consultation with a third independent reviewer (M.-S.B.).

We collected data on the reasons for treatment, cabergoline dose, the number of pregnancies exposed in each group, the timing of exposure relative to pregnancy in the cabergoline group, and the number and percentage of major malformations and spontaneous abortions in each group if available. The authors' conclusions and *p*-values were also considered to assess whether there were statistical differences between cabergoline and other comparators in included studies. The corresponding authors of the included studies were contacted if data was missing or needed to be clarified. The data was evaluated qualitatively, as high heterogeneity between studies precluded a meta-analysis. PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) publication guidelines were followed for the writing of this article.

Two review authors independently assessed the risk of bias of the included studies. The quality of cohort studies was assessed by using the Newcastle-Ottawa Quality Assessment Scale. This scale uses a star or point system to assess selection and attrition bias (four points), intergroup comparability (two points), and exposure bias (three points) for a maximum of nine points. We used the Agency for Healthcare Research and Quality thresholds for the Newcastle-Ottawa Quality Assessment Scale and graded the study quality as good (3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome or exposure domain), fair (2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome or exposure domain) or poor (0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 star in outcome or exposure domain). Only the quality of cohort studies with a comparator group was assessed, as cohort studies without a comparator are automatically considered poor, given that the comparability domain would receive a 0 star.

The quality of randomized controlled trials was assessed by using the Cochrane Risk of Bias tool. For each study, we evaluated if there was a low risk of bias, a high risk of bias, or an unclear risk of bias regarding seven items (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective reporting, and other bias). We used the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions to make our judgment.

3 | Results

The database search identified 2186 records, which included 2099 unique records after removal of duplicates. After screening of abstracts, 2034 articles were excluded for not responding to selection criteria, leaving 65 full-text articles to be screened for

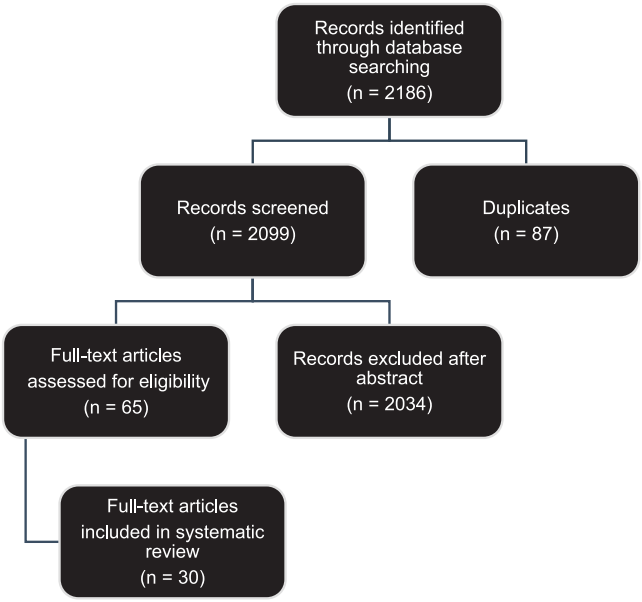

FIGURE 1 | Flow chart.

eligibility. Initially, all 65 articles could have been included in the systematic review with our inclusion criteria, but we decided to include only the 30 articles that evaluated specifically congenital malformations and/or spontaneous abortions (Figure 1).

3.1 | Observational Cohort Studies Comparing Cabergoline to Another Treatment or No Treatment

Two prospective and 10 retrospective cohort studies were identified, involving a total of 372 pregnancies exposed to cabergoline (Araujo et al. 2017; Bahceci et al. 2010; Barraud et al. 2020; Caron et al. 2010; Domingue et al. 2014; Esinler et al. 2013; Galvão et al. 2017; Hosseini et al. 2011; Karaca et al. 2018; Lebbe et al. 2010; O'Sullivan et al. 2020; Tanrikulu and Yarman 2021) (Table 1). The median age of mothers during gestation was 31 years old (range: 28–34). The indication for using cabergoline was mainly hyperprolactinoma or prolactinoma. In the two prospective studies, cabergoline was used in the prevention of OHSS, and two other studies included patients with pituitary adenomas or acromegaly (Caron et al. 2010; Karaca et al. 2018). Most pregnancies were exposed between conception and the end of the first trimester ($n = 322$). Twenty-one pregnancies were also exposed during the second trimester, third trimester, both trimesters, or for the entire duration of the pregnancy. For the remaining 29 pregnancies, the duration of exposure was not mentioned, but in all cases, patients became pregnant while on cabergoline therapy.

When reported, the median dose of cabergoline was approximately 0.5–1 mg per week (range: 0.25–4 mg/week) for endocrine disorders and 0.5 mg daily for 8 days for OHSS prevention.

Eight studies evaluated major malformations. A total of eight major malformations were reported in the cabergoline group, which represents an incidence of 2.1% (8/372). Four of the eight malformations were of the central nervous system, including two neural tube defects reported in two different trials (Karaca et al. 2018; Lebbe et al. 2010). The other two central nervous system malformations were microcephaly (Karaca et al. 2018) and rhombencephalosynapsis (Lebbe et al. 2010). Additionally, there was one case of Down syndrome (Stalldecker et al. 2010). The remaining major malformations were varied. The incidence of malformation observed in the bromocriptine group was 3.3% (16/480). All authors report no statistical difference between the cabergoline group and the comparator group for the incidence of major malformations.

Eleven of the 12 selected studies evaluated the occurrence of spontaneous abortions. The mean proportion of spontaneous abortion occurred in about 8.6% (range = 0%–30%) of pregnancies in the cabergoline group. Four studies with a small number of pregnancies had no spontaneous abortions ($n = 45$ pregnancies). The mean incidence of spontaneous abortions in the bromocriptine group was 6.5% (range = 0%–57.1%). The incidence of spontaneous abortions was variable between studies, but mostly between 0% and 21.4%. One study including 17 confirmed pregnancies following in vitro fertilization (IVF) treatment for polycystic ovaries or polycystic ovarian syndrome reported a 30% (3/10) incidence of spontaneous abortion in the cabergoline group and a 57% (4/7) incidence in the control group (Hosseini et al. 2011). All study authors report statistically similar risks of spontaneous abortions between cabergoline and the comparator group.

Corresponding authors of two included studies were contacted for missing data and to clarify tables of results (Araujo et al. 2017; Karaca et al. 2018). Their responses were integrated into the data presented in Table 1.

3.2 | Observational Cohort Studies Without a Comparator Group

Six prospective and three retrospective cohort studies including 900 pregnancies exposed to cabergoline were identified in the literature review (Auriemma et al. 2013; Cannavò et al. 1999; Ciccarelli et al. 1997; Ono et al. 2010; Rastogi et al. 2017; Ricci et al. 2002; Robert et al. 1996; Sant' Anna et al. 2020; Stalldecker et al. 2010) (Table 2). Cabergoline was used for the treatment of hyperprolactinemia or prolactinoma. All pregnancies were exposed at conception or during the first trimester. In most studies, cabergoline was discontinued upon pregnancy confirmation. In 66 pregnancies, cabergoline was continued beyond the first trimester, with only 25 of them being exposed throughout the entire duration of the pregnancy. For 61 pregnancies, patients became pregnant while on cabergoline treatment, but the duration of exposure varied from conception to full-term without specifying the number of pregnancies per trimester (Ricci et al. 2002).

The cabergoline dose used in studies varied greatly, ranging from 0.125 to 9 mg per week.

Major malformations were evaluated in the nine studies included. In total, 17 major malformations occurred among 900 pregnancies, with an incidence of 1.9%. Four studies reported normal pregnancies with no apparent malformations at birth.

TABLE 1 | Summary of prospective and retrospective studies with a comparator group.

Author, year, country and type of study	Indication	Timing of exposure for cabergoline	Cabergoline				Control		
			Pregnancies exposed	Dose (mg)	MM, *N* (%)	SA, *N* (%)	Pregnancies exposed	MM, *N* (%)	SA, *N* (%)
Tanrikulu and Yarman (2021) Turkey Retrospective	Macroprolactinoma	At conception	14	0.5–3 mg/week	NR	3 (21.4)	Bromocriptine: 20	NR	2 (10)
Barraud et al. (2020) France Retrospective	Macroprolactinoma	24 patients stopped at conception, 6 patients continued during pregnancy	30	NR	0	0	Bromocriptine: 38	1 (2.6)	2 (5.2)
O'Sullivan et al. (2020) New Zealand Retrospective	Prolactinoma	Median treatment discontinua-tion at 4.5th week of gestation 7 pregnancies continued on cabergoline for a median of 28 weeks (9–36 weeks)	41	0.25–2 mg/week	1 (2.4)	3 (7.3)	Bromocriptine: 16	1 (6.2)	3 (18.7)
Karaca et al. (2018) Turkey Retrospective	Pituitary adenoma, acromegaly, NFPA	Majority stopped at conception, 3 continued after conception (median duration: 38 weeks [8–40]) and 1 continued throughout all pregnancy	52	1 mg/week (0.25–2.5)	2 (3.8)	5 (9.6)	Bromocriptine: 36	2 (5.5)	4 (11.1)
Araujo et al. (2017) Portugal Retrospective	Prolactinoma	At conception	6	Cumulative dose: 312 mg (55–512.5 mg)	0	0	Bromocriptine: 26	1 (3.8)	1 (3.8)
Galvão et al. (2017) Portugual Retrospective	Prolactinoma	Majority discontinued by 8th week of gestation	4	0.5–1 mg/week	0	0	Bromocriptine: 21 No treatment: 10	0 0	0 0
Domingue et al. (2014) Belgium Retrospective	Prolactinoma	First trimester	36	Cumulative dose: 38 mg (6–291 mg)	0	NR	Bromocriptine: 3 Quinagolide: 1	0 0	NR

(Continues)

TABLE 1 | (Continued)

Author, year, country and type of study	Indication	Timing of exposure for cabergoline	Cabergoline				Control		
			Pregnancies exposed	Dose (mg)	MM, *N* (%)	SA, *N* (%)	Pregnancies exposed	MM, *N* (%)	SA, *N* (%)
Bahceci et al. (2010) Turkey Retrospective	Hyperprolactinoma	At conception	65	1 mg/week	NR	7 (10.8)	Bromocriptine: 65	NR	9 (13.8)
Caron et al. (2010) France Retrospective	Acromegaly	At conception	5	0.5 mg twice per week	0	0	Bromocriptine: 17	0	0
							Quinagolide: 3	0	0
							Somatostatin analogs: 14	0	2 (14.3)
							DA agonist + somatostatin analog: 8	0	0
Lebbe et al. (2010) Belgium Retrospective	Hyperprolactinoma	Cabergoline stopped after conception (median 4 weeks of gestation): 59 Cabergoline up to 10–12th week gestation: 8 Cabergoline continued beyond 1st trimester (up to 15–22 weeks): 4	100	Mean 3.6 ± 4.7 mg (median 2 mg; range: 0.5–38 mg)	5 (5)	10 (10)	No treatment: 173	11 (6.3)	NR
Esinler et al. (2013) Turkey Prospective	IVF at risk of OHSS	At conception	9	Daily dose: 0.5 mg	NR	1 (11.1)	Coasting: 22	NR	4 (18.1)
Hosseini et al. (2011) Iran Prospective	IVF at risk of OHSS	At conception	10	Dose every other day: 1 mg	NR	3 (30)	Usual protocol: 7	NR	4 (57.1)
Total			372		8 (2.1)	32 (8.6)	480	16 (3.3)	31 (6.5)

Abbreviations: MM, major malformations; N/A, not applicable; NR, not reported; SA, spontaneous abortions.

TABLE 2 | Summary of prospective and retrospective studies without a comparator group.

Author, year and country and type of study	Indication	Timing of exposure for cabergoline	Cabergoline			
			Pregnancies exposed	Dose (mg)	MM, *N* (%)	SA, *N* (%)
Sant' Anna (2020) Brazil Retrospective	Prolactinoma	First trimester: 156, median 10 weeks (2–11) Continued after first trimester: 38 NR: 39 (at least during conception)	233	1 mg/week (0.125–3.5)	7 (3)	14 (7.5%) when stopped at pregnancy confirmation 12 (38%) when continued throughout pregnancy
Stalldecker et al. (2010) Argentina Retrospective	Hyperprolactinoma	First trimester: 96.9% of pregnancies (median 4 weeks after conception) First and second trimesters: 3.1%	103	0.125–5 mg/week	1 (1)	7 (6.8)
Robert et al. (1996) International Retrospective	Hyperprolactinoma	1–144 days of gestation	226 (204 with reported information on outcomes)	0.125–4 mg/week	4 (2.4)	24 (11.7)
Rastogi et al. (2017) India Prospective	Prolactinoma	Group A: continued during pregnancy Group B: until 4–12 weeks of gestation	A: 25 B: 23	Mean cumulative dose: A: 52.1 ± 42.7 mg B: 14.1 ± 14.7 mg	A: 3 (12) B: 0 (0) Total: 6.3%	A: 3 (12) B: 1 (4.3)
Auriemma et al. (2013) Italy Prospective	Hyperprolactinemia	Until confirmation of pregnancy (maximum 6 weeks of gestation)	143	0.69 ± 0.35 mg/week (median: 0.5)	0 (0)	13 (9.1)
Ono et al. (2010) Japan Prospective	Prolactinoma	Until confirmation of pregnancy (maximum 4 weeks of gestation)	93	2.29 ± 2.16 mg/week (0.25–9.0)	0	1 (1.1)
Ricci et al. (2002) Italy Prospective	Hyperprolactinemia	At conception, duration variable (from conception to full term)	61	1.1 mg/week (0.25–7.0)	2 (3)	6 (9.8)
Cannavò et al. (1999) Italy Prospective	Prolactinoma	Until 12 weeks of gestation	6	Initial: 0.5 mg/week Maximum: 3.5 mg/week	0	1 (16.7)
Ciccarelli et al. (1997) Italy Prospective	Hyperprolactinemia	Until confirmation of pregnancy (week not reported)	9	0.25–3.5 mg/week	0	1 (11.1)
Total			900		17 (1.9)	83 (9.2)

Abbreviations: HES, hydroxyethyl starch; IVF, in vitro fertilization; MM, major malformations; N/A, not applicable; NR, not reported; OHSS, ovarian hyperstimulation syndrome; SA, spontaneous abortions.

The other five studies reported the 17 major malformations, including five chromosomal anomalies (three Down syndrome, trisomy 18, 18p deletion syndrome), six central nervous system malformations (four neural tube defects, hydrocephaly with cerebral atrophy, scaphocephaly), two tetralogy de Fallot (one of them had also a neural tube defect which was mentioned previously), 2 unknown malformations, and three other different malformations.

Spontaneous abortion was reported in all studies and ranged from 1% to 12% for most of them. One study including 233 confirmed pregnancies in patients with prolactinoma reported a 7.5% incidence of spontaneous abortions in patients who stopped cabergoline at pregnancy discovery compared to a 38% rate for patients continuing treatment during pregnancy (Sant' Anna et al. 2020). Another study reported a 16.7% (1/6) incidence of spontaneous abortion in patients treated for prolactinoma with cabergoline (Cannavò et al. 1999).

3.3 | Randomized Controlled Trials

Nine randomized controlled trials were found (Bassiouny et al. 2018; Carizza et al. 2008; Elnory and Elmantwe 2018; Fouda et al. 2016, 2022; Jellad et al. 2017; Matorras et al. 2013; Shaltout et al. 2012; Zahran et al. 2018) (Table 3). Cabergoline was compared to calcium infusion, coasting, clomiphene citrate (CC), hydroxyethyl starch infusion (HES), a combination cabergoline/antagonist rescue with cetrorelix, or to a stimulating protocol for IVF only. No randomized studies compared cabergoline to bromocriptine.

In all studies except one (Zahran et al. 2018), cabergoline was used to prevent OHSS in high-risk patients undergoing IVF treatment cycles. In the other study (Zahran et al. 2018), cabergoline was used to induce ovulation in infertile euprolactinemic patients with polycystic ovary syndrome. A total of 390 pregnancies were exposed to cabergoline alone or combined with coasting, CC, HES, or stimulating protocol for IVF. Most of them were exposed during 7–8 days, beginning the day of hCG administration or the ovum pick-up (OPU), except for one study (Zahran et al. 2018) which began on Day 3 of the cycle for 9 days to induce ovulation with CC. Considering that these studies were mainly interested in efficacy data and rarely about safety data, only one looked at major and minor malformations, but none occurred (Shaltout et al. 2012). Spontaneous abortions were reported in all articles, and all authors concluded a normal rate of spontaneous abortions of 3%–17% with cabergoline compared to other comparators.

3.4 | Evaluation of Study Quality

For observational cohort studies, the overall quality of the studies is poor (Table 4). For 10 out of 12 studies, authors did not compare the population characteristics between their treatment groups or groups that were significantly different regarding risk factors that could affect major malformations or spontaneous abortion risks, such as maternal age, BMI, maternal history of spontaneous abortions, and IVF rate. In addition, there were no adjustments for these confounding factors, which have a negative impact on comparability between groups. As a result, these trials received a score of 0 stars in the comparability domain of the Newcastle-Ottawa Quality Assessment Scale, indicating a high risk of bias. The two other studies (Esinler et al. 2013; Hosseini et al. 2011) were of good quality according to the scale. However, these studies evaluated spontaneous abortions only and were conducted on small sample sizes (9 and 10 pregnancies exposed to cabergoline, respectively). The trials lacked sufficient statistical power to detect a difference between groups.

The randomized controlled trials were at low risk of bias for most items in the Cochrane Risk of Bias tool (Table 5). Authors used a computer random number generator for randomization, and randomization was concealed in sealed opaque envelopes. Participants were not blinded to treatment, but outcome assessors were blinded in some cases, and outcomes were objective. Accordingly, it is unlikely that unblinding would have impacted the trial results. Participants between groups were comparable in their characteristics, and no participant was lost to follow-up. However, we considered all studies at high risk of bias for the "other bias" criteria. Since spontaneous abortions were always evaluated as secondary outcomes, there was a low number of pregnant participants, no adjustment for multiplicity of testing, and a lack of statistical power. Therefore, even if general quality was good for these trials, we considered that the quality for the results on spontaneous abortion rates specifically was poor.

4 | Discussion

The studies included in the present systematic review vary in terms of population studied, exposure to cabergoline, and duration of follow-up. We found reassuring data for the use of cabergoline in pregnancy for the 1662 total exposures regrouped in this review, and for which outcomes were available.

Major congenital malformation rates after exposure to cabergoline at conception or during the first trimester were evaluated in 17 observational trials and one randomized controlled trial, comprising a total of 1216 pregnancies. Overall, most studies reported similar risks of congenital malformations between cabergoline and other comparators or no treatment in pregnant patients. For studies without comparators, the incidence of major malformations was comparable to the expected incidence in the general population. The rate of major malformations generally found in the population is around 2%–3% (Moore et al. 2013). One trial by Rastogi et al. (2017) taking place in India reported a malformation rate of 6.3%, which is higher than the expected rate in the general population. Among 25 exposed pregnancies, all three were neural tube defects. The authors report that this percentage is similar to the malformation rate in India. On the other hand, a systematic review and meta-analysis published in 2018 (Bhide and Kar 2018) calculated a normal rate of 2%–3% in India for major malformations, but it is also mentioned that this percentage is probably underestimated since there is a lack of a birth defects surveillance program and infantile mortality is high. Central nervous system defects are the type of major malformation with the highest prevalence in India according to this study and could be prevented with preconception folic acid supplementation. Considering the limited number of patients included in

TABLE 3 | Summary of randomized controlled studies.

Author, year and country	Indication	Timing of exposure	Cabergoline				Control group		
			Pregnancies exposed	Dose (mg)	MM, *N* (%)	SA, *N* (%)	Comparators (pregnancies exposed)	MM, *N* (%)	SA, *N* (%)
Fouda et al. (2022), Egypt	IVF at risk for OHSS	The day of hCG administration for 8 days	28	0.5 mg/day	NR	4 (14.3)	Calcium infusion intravenous calcium gluconate (10%, 10 mL in 200 mL of physiologic saline) was administered daily for 4 days starting on the day of ovum pickup: 30	NR	4 (13.3)
Elnory and Elmantwe (2018), Egypt	IVF at risk for OHSS	The day of OPU for 7 days	58	0.5 mg/day	NR	10 (8.7) patients exposed and (17) pregnancies	Calcium infusion intravenously on the day of OPU and day 1, 2 and 3 after OPU over 30 min: 60	NR	15 (13) patients exposed and 15 (25) pregnancies
Bassiouny (2018), Egypt	IVF at risk for OHSS	The day of hCG administration for 8 days	Cabergoline (A): 49 Cabergoline + coasting (B): 56	0.25 mg/day	NR	A: 8 (16.3) B: 8 (14.3)	Coasting (C): 46	NR	6 (13)
Zahran et al. (2018), Egypt	Induction of ovulation in infertile eupro-lactinemia patients with polycystic ovary syndrome	Beginning on Day 3 of the cycle for 9 days	Cabergoline + Clomiphene citrate (CC): 19	0.25 mg PO qid Days 3, 6, 9 of each cycle for 3 cycles	NR	3 (15.8)	CC alone: 8	NR	2 (25)
Fouda et al. (2016), Egypt	IVF at risk for OHSS	The day of hCG administration for 8 days	42	0.5 mg/day	NR	5 (11.9)	Cabergoline + antagonist rescue: 46 (Cetrorelix acetate 0.25 mg S.C daily until and including the day of HCG administration)	NR	5 (10.9)
Jellad et al. (2017), Tunisia	IVF at risk for OHSS	Starting from hCG administration day for 7 days	Cabergoline + stimulating protocol for IVF: 20	0.5 mg/day	NR	3 (15)	Stimulating protocol for IVF only: 14	NR	4 (28.6)

(Continues)

TABLE 3 | (Continued)

Author, year and country	Indication	Timing of exposure	Cabergoline				Control group		
			Pregnancies exposed	Dose (mg)	MM, *N* (%)	SA, *N* (%)	Comparators (pregnancies exposed)	MM, *N* (%)	SA, *N* (%)
Matorras et al. (2013), Spain	IVF at risk of OHSS	Starting from hCG administration day for 8 days	Cabergoline + HES infusion: 43	0.5 mg/day	NR	5 (11.6)	HES infusion only: 48	NR	9 (18.8)
Shaltout et al. (2012), Egypt	IVF at risk for OHSS	The day of hCG administration for 8 days	Cabergoline + stimulating protocol for IVF: 42	0.25 mg/day	0	5 (11.9)	Stimulating protocol for IVF only: 41	0	5 (12.2)
Carizza et al. (2008), Brazil	IVF at risk for OHSS	The day after oocyte retrieval for 3 weeks	Cabergoline + stimulating protocol for IVF: 33	0.5 mg/day	NR	1 (3)	Stimulating protocol for IVF only: 32	NR	3 (9.3)
Total			390		0	52 (13.3)	325	0	53 (16.3)

Abbreviations: IVF, in vitro fertilization; MM, major malformations; NR, not reported; OHSS, ovarian hyperstimulation syndrome; OPU, ovum pick-up; SA, spontaneous abortions.

the trial by Rastogi et al. and the lack of national guidelines on folic acid supplementation during pregnancy in India, the 6.3% malformation rate could represent a falsely high rate. Even if the malformation rate was higher in this study, it was still included in our systematic review since the authors reported no statistical difference with bromocriptine in the same population.

A higher-than-expected number of neural tube defects and other central nervous system malformations was mentioned in some studies. Six neural tube anomalies occurred in 1174 exposed pregnancies, which includes the three that occurred in the Rastogi et al. trial. This represents five cases per 1000 live births, which is higher than the rate in the general population of one to four cases per 1000 live births (Canadian Paediatric Society 1995). Even with these reports of central nervous system malformations following cabergoline use in pregnancy, it is not possible to conclude on the teratogen risk of cabergoline considering the high heterogeneity and risk of bias from other potential confounders in the included studies.

Spontaneous abortion rates were reported by 21 observational trials and eight randomized controlled trials for a total of 1626 pregnancies. Most studies found no difference in spontaneous abortion risk between patients taking cabergoline during pregnancy and those not taking cabergoline. Percentages obtained were either lower or similar to the 10%–20% miscarriage risk found in the general population (Moore et al. 2013). Three observational studies reported higher rates of miscarriage. The trial by Tanrikulu and Yarman (2021) found a 14.7% rate of miscarriage in pregnancies exposed to cabergoline or bromocriptine. When we calculate the percentage of spontaneous abortions in the cabergoline group only, the rate is higher (21%) than what is expected in the general population (Moore et al. 2013) and higher than the 10% in the bromocriptine group. However, a low number of pregnancies occurred under cabergoline in this study. Therefore, we cannot exclude a significant result by coincidence. The trial by Sant' Anna et al. (2020) found a rate of spontaneous abortions of 7.5% when patients discontinued cabergoline at pregnancy confirmation and of 38.7% in patients who continued cabergoline throughout pregnancy. The 38.7% rate with cabergoline is higher than the maximum rate of miscarriage found in the bromocriptine group (18.7%). It is not possible to draw a conclusion on the risk of miscarriage with cabergoline because only 31 pregnant patients continued their treatment during pregnancy; authors mention that there is underreporting of miscarriages in Brazil and other confounding factors that could have influenced miscarriage rates were not evaluated. Another study reported a higher spontaneous abortion rate of 30% (3/10) (Hosseini et al. 2011) compared to the normal rate in the general population. However, the number of pregnancies in this study is small, and patients were undergoing IVF treatment for polycystic ovaries or polycystic ovarian syndrome and were therefore possibly at higher risk of spontaneous abortion. The abortion rate in the control group was 57%. The authors did not report if the abortions reported were spontaneous or voluntary pregnancy terminations. Overall, cabergoline does not seem to increase the risk of spontaneous abortion compared to other comparators such as bromocriptine or no treatment.

Even if all included studies did not report an increased risk of major malformations or spontaneous abortions when pregnant

TABLE 4 | Newcastle–Ottawa quality assessment scale for observational cohort studies with comparators.

	Trials											
	Araujo	**Bahceci**	**Barraud**	**Caron**	**Domingue**	**Esinler**	**Galvao**	**Hosseini**	**Karaca**	**Lebbe**	**O'Sullivan**	**Tanrikulu**
Quality assessment	**2017**	**2010**	**2020**	**2010**	**2014**	**2013**	**2017**	**2011**	**2018**	**2010**	**2020**	**2021**
Representative of the exposed cohort	*	*	*	*	*	*	*	*	*	*	*	*
Selection of external cohort	*	*	*	*	*	*	*	*	*	*	*	*
Ascertainment of exposure	*	*	*	*	*	*	*	*	*	*	*	*
Outcome of interest not present at the start of the study	*	*	*	*	*	*	*	*	*	*	*	*
Comparability of cohorts: Main factor	0	0	0	0	0	*	0	*	0	0	0	0
Comparability of cohorts: Additional factor	0	0	0	0	0	*	0	*	0	0	0	0
Assessment of outcomes	*	*	*	*	*	*	0	*	*	*	*	*
Sufficient follow-up time	*	0	*	*	*	*	0	0	*	*	*	*
Adequacy of follow-up	0	0	*	0	*	0	*	*	0	*	0	*
Quality status	Poor	Poor	Poor	Poor	Poor	Good	Poor	Good	Poor	Poor	Poor	Poor

Note: * = criterion is met (high quality), 0 = criterion is not met (low quality).

TABLE 5 | Cochrane risk of bias tool for randomized controlled trial.

	Trials								
	Bassiouny	Carizza	Elnory	Fouda	Fouda	Jellad	Matorras	Shaltout	Zahran
Quality assessment	2017	2008	2018	2016	2022	2017	2013	2012	2017
Random sequence allocation (selection bias)	⊕	⊕	⊕	⊕	⊕	?	⊕	⊕	⊕
Allocation concealment (selection bias)	⊕	⊕	⊕	⊕	⊕	?	⊕	?	⊕
Blinding of participants and personnel (performance bias)	⊕	⊕	⊕	⊕	⊕	?	⊕	?	⊕
Blinding of outcome assessment (detection bias)	⊕	⊕	⊕	⊕	⊕	⊕	⊕	?	⊕
Incomplete outcome data (attrition bias)	⊕	⊕	⊕	⊕	⊕	?	⊕	⊕	?
Selective reporting (reporting bias)	⊕	?	⊕	⊕	⊕	?	⊕	?	?
Other sources of bias	⊖	⊖	⊖	⊖	⊖	⊖	⊖	⊖	⊖

patients were exposed to cabergoline during the first trimester, the quality of the data is considered poor (Tables 4 and 5) and the results are at high risk of bias. However, 1662 pregnancies exposed to cabergoline are a considerable number of exposures, considering that only 684 and 266 exposures, respectively, are needed to detect a twofold increased risk of major malformations and spontaneous abortions with 80% power and a 95% confidence interval. Given the rarity of central nervous system malformations, approximately 17,000 exposures are required in each group to detect a twofold increased risk of malformations. A definite conclusion on the subject cannot be made. Other high-quality trials are needed to conclude with a better certainty.

Based on data from more than 6000 pregnancies, bromocriptine is considered the best-known DA agonist during pregnancy. With a risk of major malformations and spontaneous abortions similar to that of the general population, its use is considered safe, regardless of the trimester of pregnancy (Tritos and Miller 2023). However, bromocriptine has more adverse effects (especially nausea, orthostatic hypotension and headache) than cabergoline (Rains et al. 1995).

Considering the absence of available expert recommendations and guidelines in the literature, this study may help guide clinicians and patients in their choice when evaluating possible continuation of treatment with cabergoline during pregnancy. Current general practice involves interrupting treatment with cabergoline upon confirmation of pregnancy due to perceived safety risks. However, the data presented in this study suggest similar outcomes on congenital malformations and spontaneous abortions when comparing cabergoline use during pregnancy to other comparators. Cabergoline can be taken less often due to its long half-life and has a better tolerability profile, which may increase treatment satisfaction and adherence in pregnant patients requiring DA agonist treatment.

4.1 | Strengths and Limitations

The data in this systematic review was based on exhaustive research of the literature until October 2022. The population was very varied, and a great number of maternal conditions in which cabergoline can be a choice of treatment were represented. In this context, the conclusion of this study can be generalized to all pregnant patients. In practice, cabergoline is generally stopped when pregnancy is diagnosed since information on the safety of cabergoline use during pregnancy is limited.

On the other hand, studies included were of low quality and there was significant heterogeneity in participants, cabergoline dose, moment of pregnancy exposure, duration of treatment, and indication of treatment between groups. There was a limited number of patients per study and no adjustments for potential confounders such as maternal age, pregnancy history, maternal condition, health habits, comorbidity, and other medications. Also, differences between groups could be the result of varying clinical practice between physicians in different centers and/or countries.

5 | Conclusion

To the best of our knowledge, this systematic review presents the only current overview of data available for the use of cabergoline during pregnancy. Despite the lack of high-quality data, the overall review of publications seems reassuring for major

malformations and spontaneous abortions for more than 1600 exposures at conception or during the first trimester of pregnancy. A large randomized controlled study comparing cabergoline to bromocriptine would help to conclude with better certainty on the safety of cabergoline use during pregnancy. Additional data evaluating specifically the risk of central nervous system malformations with cabergoline use, other pregnancy outcomes such as prematurity, low weight for gestational age, and studies evaluating long-term neurological development of children exposed in utero would also add crucial information for the clinical decision-making process.

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Anne-Sophie Otis, Marie-Sophie Brochet, and Zoë Tremblay. The first draft of the manuscript was written by Anne-Sophie Otis, Marie-Sophie Brochet, and Zoë Tremblay, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

Marie-Sophie Brochet receives honoraria for presentations about infertility and related pharmacotherapy at laboratoire RIVA, but there is no link between this pharmaceutical company and the subject of this manuscript. Elias M. Dahdouh receives honoraria for presentations at Ferring Canada and Organon, two pharmaceutical companies. All other authors declare no conflicts of interest. The authors have no relevant nonfinancial interests to disclose.

Data Availability Statement

All data is present in the manuscript or the Supporting Information. There is no shared data linked to this work.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.