National Institute for Health and Care Excellence

Draft for consultation

Fertility problems: assessment and treatment

[F] Cabergoline for hyperprolactinaemia

NICE guideline NGXXX

Evidence reviews underpinning recommendation 1.5.12 in the NICE guideline

September 2025

Draft for consultation

This evidence review was developed by NICE

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

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ISBN:

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Cabergoline for hyperprolactinaemia

Review question

What is the clinical and cost effectiveness of cabergoline for fertility problems associated with hyperprolactinaemic amenorrhoea or oligomenorrhea?

Introduction

Hyperprolactinaemia can lead to menstrual irregularities, with infrequent, irregular or absent periods. Ovulation may not occur or may occur infrequently or irregularly. This condition may therefore be associated with a reduction in fertility. Secretion of prolactin from the pituitary is inhibited by dopamine released from the hypothalamus. Dopamine agonists therefore provide a logical therapeutic option to treat hyperprolactinaemia. Bromocriptine is currently recommended by NICE for this indication but has a number of common side-effects, and cabergoline has been increasingly used in clinical practice.

The aim of this review is to determine if cabergoline is effective at improving fertility in people with hyperprolactinaemic amenorrhoea or oligomenorrhea.

Summary of the protocol

See Table 1 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	People with a health-related female factor fertility problem associated with hyperprolactinaemic amenorrhoea (no periods) or oligomenorrhea (infrequent periods) In this guideline, people with health-related fertility problems are those who have a known health-related impediment to fertility, or those who do not achieve a pregnancy: • after 12 months of regular unprotected sexual intercourse or • after 6 cycles of artificial insemination
Intervention	• Cabergoline
Comparison	• Placebo • Other dopamine agonists (e.g. bromocriptine) • No intervention
Outcome	**Critical** • Live birth • Viable intrauterine pregnancy confirmed by ultrasound (accounting for singleton pregnancy, twin pregnancy, and higher multiple pregnancy) **Important** • Miscarriage • Gestational age at delivery • Birth weight • Major congenital anomaly • Ovulation rate

For further details see the review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document (supplementary document 1).

Declarations of interest were recorded according to NICE's conflicts of interest policy.

Effectiveness evidence

Included studies

Two randomised controlled trials (RCTs) were included for this review (Motazedian 2010, Webster 1994). Both studies compared cabergoline to bromocriptine.

The included studies are summarised in Table 2.

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

Studies not included in this review are listed, and reasons for their exclusion are provided in appendix J.

Summary of included studies

Summaries of the studies that were included in this review are presented in Table 2.

Table 2: Summary of included studies.

Study	Population	Intervention	Comparison	Outcomes	Comments
Motazedian 2010 RCT Iran	N=183 hyperprolactinaemic infertile women undergoing induction of ovulation for intrauterine insemination Mean age (SD): 28.9 (4.4) years Mean duration of infertility (SD): 4.5 (1.9) years	Cabergoline 0.25mg twice per week Duration: Unclear	Bromocriptine 2.5mg twice per day Duration: Unclear	• Pregnancy	90.2% of the participants had irregular menstruation (oligomenorrhoea) Whilst duration of intervention was unclear, pregnancy was documented at 6-7 weeks gestational age.
Webster 1994 RCT Europe and Argentina	N=459 hyperprolactinaemic women with amenorrhoea Mean age (SD): 31 (7) years Duration of infertility not reported	Cabergoline 0.5 to 1.0mg twice weekly Duration: 24 weeks	Bromocriptine 2.5 to 5.0mg twice daily Duration: 24 weeks	• Ovulation rate • Composite outcome of complete clinical success	Pregnancy not reported as an outcome as during weeks 1-8, women at risk of becoming pregnant were advised to use barrier contraception, but in weeks 9-24 only those taking

Study	Population	Intervention	Comparison	Outcomes	Comments
					cabergoline were advised to continue such measures. Treatment was stopped if pregnancy was confirmed.

mg: milligrams; RCT: randomised controlled trial; SD: standard deviation.

See the full evidence tables in appendix D. No meta-analysis was conducted (and so there are no forest plots in appendix E).

Summary of the evidence

There was some very low quality evidence showing higher pregnancy (measured using transvaginal sonography at 6-7 weeks of gestational age) in hyperprolactinaemic infertile women with oligomenorrhoea receiving cabergoline relative to bromocriptine. There was also some potentially indirect very low quality evidence (as it was unclear that participants had a health-related fertility problem) for a benefit of cabergoline relative to bromocriptine for hyperprolactinaemic women with amenorrhoea for a composite outcome of complete clinical success (which included the occurrence of at least 2 consecutive menses with biochemical evidence of ovulation on at least 1 occasion or pregnancy). This study also found a statistically significant benefit for cabergoline relative to bromocriptine when the outcome of ovulation rate was measured as at least 1 ovulatory cycle, although this effect estimate was just below the threshold for a clinically important benefit. All other outcomes in the protocol were not reported by any studies, including live birth, miscarriage, gestational age at delivery, birth weight, and major congenital anomaly.

See appendix F for full GRADE tables.

Economic evidence

A total of 169 studies were identified in the health economic literature search for this review question. After duplicates were removed, 139 studies were sifted on title and abstract. Of these 139 studies all were excluded at this stage.

Included studies

A systematic review of the economic literature was conducted but no economic studies were identified which were applicable to this review question.

Also see the literature search strategy in appendix B and the economic study selection flow chart in appendix G.

Excluded studies

Economic studies not included in this review are listed, and reasons for their exclusion are provided in appendix J.

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation.

Unit costs

Resource	Unit costs	Weekly cost	Source
Cabergoline 500microgram tablets	£4.37	£8.75 [a]	NHS Drugs Tariff, accessed December 2024 https://www.drugtariff.nhsbsa.nhs.uk/#/00446515-DC_2/DC00446029/Part%20VIIIA%20products%20C
Bromocriptine 2.5mg tablets	£2.50	£35.00 [b]	NHS Drugs Tariff, accessed December 2024 https://www.drugtariff.nhsbsa.nhs.uk/#/00429017-DC/DC00428327/Part%20VIIIA%20products%20B

a) *Based on a dose of 2 x 500 micrograms per week*
b) *Based on a dose of 2 x 2.5 mg per day*

The committee's discussion and interpretation of the evidence

The outcomes that matter most

Live birth and viable intrauterine pregnancy confirmed by ultrasound were prioritised as critical outcomes by the committee. They were selected as the best indicators of fertility and were specified in the core outcome set for fertility research (Duffy 2020).

Miscarriage, gestational age at delivery, birth weight, major congenital anomaly and ovulation rate were identified as important outcomes by the committee. Miscarriage was prioritised as an important outcome as it provides meaningful information about the success of a pregnancy and can have a significant impact on the woman's psychological and physical health. Gestational age at delivery, birth weight and major congenital anomaly were prioritised as important outcomes as they provide further information on the potential harms to babies. Since hyperprolactinaemia is a cause of ovulatory dysfunction, the committee prioritised ovulation rate as an important outcome.

The quality of the evidence

The quality of the evidence was assessed with GRADE and rated as low to very low quality.

The evidence was downgraded for risk of bias because of unclear allocation concealment and an apparent lack of blinding either partially or throughout the study period. There were also concerns about the timing of outcome assessment or the selection of the reported result, and either no information was available on any deviations from the intended interventions, or it was likely that deviations from the intended interventions had occurred. The evidence was also downgraded for imprecision due to the 95% confidence interval crossing a threshold for minimally important difference and for indirectness in one study because it was not clear whether the population met the inclusion criteria, and in another study because the intervention included the administration of clomifene citrate and human menopausal gonadotropin which is not usual practice.

There were no concerns about inconsistency, or publication bias in the evidence.

Benefits and harms

The committee noted that no evidence was identified that reported live birth as an outcome.

The committee discussed the evidence showing that cabergoline was associated with a higher rate of pregnancy (measured using transvaginal sonography at 6-7 weeks of gestational age) compared to bromocriptine for hyperprolactinaemic infertile women

with oligomenorrhoea. The committee also considered potentially indirect evidence (as it was unclear whether participants had a health-related fertility problem) showing a benefit of cabergoline relative to bromocriptine for hyperprolactinaemic women with amenorrhoea for a composite outcome of complete clinical success (which included the occurrence of at least 2 consecutive menses with biochemical evidence of ovulation on at least 1 occasion or pregnancy). There was also a statistically significant benefit from this study for the outcome of at least 1 ovulatory cycle (in women whose menses resumed and in whom plasma progesterone was measured at least once at 24 weeks) but this did not meet the criteria for a clinically important difference.

The committee discussed that bromocriptine is currently recommended by NICE and used to treat hyperprolactinaemia but that the evidence had shown that cabergoline may be a more effective option and so they recommended cabergoline be used instead of bromocriptine. The committee also noted, based on their knowledge and experience, that bromocriptine was more likely to cause side effects such as hypotension, nausea and vomiting and headache, and could not be tolerated by some people, so that the use of cabergoline may lead to less discontinuation. The committee also noted that bromocriptine needs to be taken once or twice daily, while cabergoline is administered as a once or twice weekly dose, so this would also be more convenient to people prescribed it as treatment for their hyperprolactinaemia.

Cost effectiveness and resource use

This review question was not prioritised for economic analysis and therefore the committee made a qualitative assessment of the likely cost-effectiveness of their recommendations. The committee were aware that weekly cabergoline is less expensive than daily bromocriptine. Despite the lack of evidence on the outcome of live births, evidence on other outcomes and side effects suggested that carbergoline was more effective. Given the substantially lower costs the committee concluded that carbergoline was more cost-effective than bromocriptine for the treatment of hyperprolactinaemia which supported their recommendation. As this represents a change from previous NICE guidance the committee expected, because of the lower weekly cost of cabergoline, that there would be some savings to the NHS from their recommendation.

Recommendations supported by this evidence review

This evidence review supports recommendation 1.5.12.

References – included studies

Effectiveness

Motazedian 2010

Motazedian, Shahdokht, Babakhani, Lida, Fereshtehnejad, Seyed-Mohammad et al. (2010) A comparison of bromocriptine & cabergoline on fertility outcome of hyperprolactinemic infertile women undergoing intrauterine insemination. The Indian journal of medical research 131: 670-4.

Webster 1994

Webster, J, Piscitelli, G, Polli, A et al. (1994) A comparison of cabergoline and bromocriptine in the treatment of hyperprolactinemic amenorrhea. Cabergoline Comparative Study Group. The New England journal of medicine 331(14): 904-9.

Other

Duffy 2020

Duffy JM, AlAhwany H, Bhattacharya S, Collura B, Curtis C, Evers JL, Farquharson RG, Franik S, Giudice LC, Khalaf Y, Knijnenburg JM. (2020) Developing a core outcome set for future infertility research: an international consensus development study. Human Reproduction 35(12): 2725-34.

Appendices

Appendix A Review protocols

Review protocol for review question: What is the clinical and cost effectiveness of cabergoline for fertility problems associated with hyperprolactinaemic amenorrhoea or oligomenorrhea?

Table 3: Review protocol

ID	Field	Content
0.	PROSPERO registration number	CRD42023402311
1.	Review title	Clinical and cost effectiveness of cabergoline for fertility problems associated with hyperprolactinaemic amenorrhoea or oligomenorrhea
2.	Review question	What is the clinical and cost effectiveness of cabergoline for fertility problems associated with hyperprolactinaemic amenorrhoea or oligomenorrhea?
3.	Objective	To determine the clinical and cost effectiveness of cabergoline as a treatment for female factor fertility problems associated with hyperprolactinaemic amenorrhoea or oligomenorrhea.
4.	Searches	The following databases will be searched: Clinical searches Cochrane Central Register of Controlled Trials (CENTRAL) Cochrane Database of Systematic Reviews (CDSR) Embase MEDLINE ALL Epistemonikos Economic searches MEDLINE ALL Embase International Network of Agencies for Health Technology Assessment (INAHTA)

ID	Field	Content
		HTA Economic evaluations and quality of life filters will be applied. Searches will be restricted by: English language Human studies The full search strategies for MEDLINE database will be published in the final review. For each search, the principal database search strategy is quality assured by a second information scientist using an adaptation of the PRESS 2015 Guideline Evidence-Based Checklist.
5.	Condition or domain being studied	Treatments for female factor fertility problems associated with hyperprolactinaemic amenorrhoea or oligomenorrhea
6.	Population	Inclusion: • People with a health-related female factor fertility problem associated with hyperprolactinaemic amenorrhoea (no periods) or oligomenorrhea (infrequent periods) In this guideline, people with health-related fertility problems are those who have a known health-related impediment to fertility, or those who do not achieve a pregnancy: • after 12 months of regular unprotected sexual intercourse or • after 6 cycles of artificial insemination.
7.	Intervention	• Cabergoline
8.	Comparator	• Placebo • Other dopamine agonists (e.g. bromocriptine) • No intervention
9.	Types of study to be included	Include published full-text papers: • Systematic reviews of RCTs • Parallel RCTs (individual or cluster) If no RCT evidence: • Experimental studies using a non-randomly assigned control group design with match comparison or another method of controlling for confounding variables

ID	Field	Content
10.	Other exclusion criteria	Other exclusion criteria: • Language limitations: studies published not in English-language • Conference abstracts will not be included because these do not typically have sufficient information to allow full critical appraisal.
11.	Context	This guidance will fully update the following NICE guideline: Fertility problems: assessment and treatment (last updated 2017; CG156)
12.	Primary outcomes (critical outcomes)	• Live birth • Viable intrauterine pregnancy confirmed by ultrasound (accounting for singleton pregnancy, twin pregnancy, and higher multiple pregnancy)
13.	Secondary outcomes (important outcomes)	• Miscarriage • Gestational age at delivery • Birth weight • Major congenital anomaly • Ovulation rate
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Dual sifting will be performed on at least 10% of records; 90% agreement is required. Disagreements will be resolved via discussion between the two reviewers, and consultation with senior staff if necessary. Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. A standardised form will be used to extract data from studies. The following data will be extracted: study details (reference, country where study was carried out, type and dates), participant characteristics, inclusion and exclusion criteria, details of the interventions if relevant, setting and follow-up, relevant outcome data and source of funding. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer.
15.	Risk of bias (quality) assessment	Quality assessment of individual studies will be performed using the following checklists: • ROBIS tool for systematic reviews • Cochrane RoB tool v.2

ID	Field	Content
		The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer.
16.	Strategy for data synthesis	Depending on the availability of the evidence, the findings will be summarised narratively or quantitatively. Where possible, meta-analyses will be conducted using Cochrane Review Manager software. A fixed effect meta-analysis will be conducted and data will be presented as risk ratios or odds ratios for dichotomous outcomes, and mean differences or standardised mean differences for continuous outcomes. Heterogeneity in the effect estimates of the individual studies will be assessed using the I2 statistic. Alongside visual inspection of the point estimates and confidence intervals, I2 values of greater than 50% and 80% will be considered as significant and very significant heterogeneity, respectively. Heterogeneity will be explored as appropriate using sensitivity analyses and pre-specified subgroup analyses. If heterogeneity cannot be explained through subgroup analysis then a random effects model will be used for meta-analysis, or the data will not be pooled. The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/ Importance and imprecision of findings will be assessed against minimally important differences (MIDs). The following MIDs will be used: Live birth: statistical significance Validated scales/continuous outcomes: +/- 0.5x pooled control group SD for mean difference and SMD -0.5/0.5 for standardised mean difference. All other outcomes: 0.8 and 1.25 for all relative dichotomous outcomes; +/- 0.5x pooled control group SD for mean difference and SMD -0.5/0.5 for standardised mean difference
17.	Analysis of sub-groups	Evidence will be sub-grouped by the following only in the event that there is significant heterogeneity in outcomes: Age • <35 years • ≥35-39 years • ≥40-42 years • >42 years Where evidence is subgrouped the committee will consider on a case-by-case basis if separate recommendations should be made for distinct groups. Separate recommendations may be made where there is evidence of a differential effect of interventions in distinct groups. If there is a lack of evidence in one group, the committee will consider, based on their experience, whether it is reasonable to extrapolate and assume the interventions will have similar effects in that group compared with others.

ID	Field	Content		
18.	Type and method of review	☒	Intervention	
		☐	Diagnostic	
		☐	Prognostic	
		☐	Qualitative	
		☐	Epidemiologic	
		☐	Service Delivery	
		☐	Other (please specify)	
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	January 2023		
22.	Anticipated completion date	November 2024		
23.	Stage of review at time of this submission	Preliminary searches		
		Piloting of the study selection process		
		Formal screening of search results against eligibility criteria		
		Data extraction		
		Risk of bias (quality) assessment		
		Data analysis		
24.	Named contact	5a. Named contact Guideline Development Team A 5b. Named contact e-mail FertilityProblems@nice.org.uk 5c. Organisational affiliation of the review Guideline Development Team A, Centre for Guidelines, National Institute for Health and Care Excellence (NICE)		

ID	Field	Content
25.	Review team members	Senior Systematic Reviewer Systematic Reviewer
26.	Funding sources/sponsor	This systematic review is being completed by NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10263
29.	Other registration details	None
30.	Reference/URL for published protocol	https://www.crd.york.ac.uk/PROSPERO/view/CRD42023402311
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: notifying registered stakeholders of publication publicising the guideline through NICE's newsletter and alerts issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	Female factor fertility problems, infertility, cabergoline, hyperprolactinaemic amenorrhoea
33.	Details of existing review of same topic by same authors	None

ID	Field	Content
34.	Current review status.	
35..	Additional information	None
36.	Details of final publication	www.nice.org.uk

CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials;; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; INAHTA: International Network of Agencies for Health Technology Assessment; MID: minimally important difference; NHS: National health service; NICE: National Institute for Health and Care Excellence; PRESS: peer review of electronic search strategies; RCT: randomised controlled trial; RoB(IS): risk of bias (in systematic reviews); SD: standard deviation

Appendix B Literature search strategies

Literature search strategies for review question: What is the clinical and cost effectiveness of cabergoline for fertility problems associated with hyperprolactinaemic amenorrhoea or oligomenorrhea?

Database: Ovid MEDLINE(R) ALL 1946 to February 01, 2023

Date of last search: 02/02/2023

#	Searches
1	Hyperprolactinemia/ or Prolactinoma/
2	(hyperprolactin?emi* or HPRL).ti,ab,kf.
3	(hypersecret* or hyper secret* or ((inappropriat* or over* or high* or increase* or elevat* or excess* or raised) adj4 (prolactin or PRL or lactotropi* or luteotrop* or LTH or lactogen* or mammatropi* or milk hormone* or lactat* hormone*))).ti,ab,kf.
4	(prolactinoma? or m?croprolactinoma* or lactotroph adenoma? or (pituitary adj4 (tumo?r* or adenoma? or m?croadenoma* or growth* or neoplasm*))).ti,ab,kf.
5	or/1-4
6	menstruation disturbances/ or amenorrhea/ or oligomenorrhea/
7	(amenorrh* or amenia or oligomenorrh*).ti,ab,kf.
8	((absen* or stop* or cessation* or cease* or retention* or disorder* or disturb* or issue* or problem* or irregular* or infrequent* or inconsistent* or insufficien* or abnormal* or variation* or variable or dysfunction* or dysregulat* or deviat* or suppress* or miss* or freq* or impair* or lack* or terminat* or decreas* or return* or resum* or restor* or reappear* or regula* or normal*) adj5 (menstrua* or menses or period* or bleed* or catamenia or menarche or cycl* or gonad*)).ti,ab,kf.
9	or/6-8
10	5 and 9
11	Dopamine Agonists/ or Cabergoline/
12	(cabergolin? or CAB or cabaser or cabaseril or cabarsuss or cabest or dostinex or galastop or actualene or sogilen or sostilar or velactis).ti,ab,kf.
13	11 or 12
14	10 and 13
15	letter/
16	editorial/
17	news/
18	exp historical article/
19	Anecdotes as Topic/
20	comment/
21	case reports/
22	(letter or comment*).ti.
23	or/15-22
24	randomized controlled trial/ or random*.ti,ab.
25	23 not 24
26	animals/ not humans/
27	exp Animals, Laboratory/
28	exp Animal Experimentation/
29	exp Models, Animal/
30	exp Rodentia/
31	(rat or rats or mouse or mice or rodent*).ti.
32	or/25-31
33	14 not 32
34	limit 33 to english language

Database: Embase <1974 to 2023 February 01>

1 **Date of last search: 02/02/2023**

#	Searches
1	hyperprolactinemia/ or prolactinoma/
2	(hyperprolactin?emi* or HPRL).ti,ab,kf.
3	(hypersecret* or hyper secret* or ((inappropriat* or over* or high* or increase* or elevat* or excess* or raised) adj4 (prolactin or PRL or lactotropi* or luteotrop* or LTH or lactogen* or mammatropi* or milk hormone* or lactat* hormone*))).ti,ab,kf.
4	(prolactinoma? or m?croprolactinoma* or lactotroph adenoma? or (pituitary adj4 (tumo?r* or adenoma? or m?croadenoma* or growth* or neoplasm*))).ti,ab,kf.
5	or/1-4
6	exp "amenorrhea and oligomenorrhea"/ or menstruation disorder/
7	(amenorrh* or amenia or oligomenorrh*).ti,ab,kf.
8	((absen* or stop* or cessation* or cease* or retention* or disorder* or disturb* or issue* or problem* or irregular* or infrequent* or inconsistent* or insufficien* or abnormal* or variation* or variable or dysfunction* or dysregulat* or deviat* or suppress* or miss* or freq* or impair* or lack* or terminat* or decreas* or return* or resum* or restor* or reappear* or regula* or normal*) adj5 (menstrua* or menses or period* or bleed* or catamenia or menarche or cycl* or gonad*)).ti,ab,kf.
9	or/6-8
10	5 and 9
11	dopamine receptor stimulating agent/ or cabergoline/
12	(cabergolin? or CAB or cabaser or cabaseril or cabarsuss or cabest or dostinex or galastop or actualene or sogilen or sostilar or velactis).ti,ab,kf.
13	11 or 12
14	10 and 13
15	letter.pt. or letter/
16	note.pt.
17	editorial.pt.
18	case report/ or case study/
19	(letter or comment*).ti.
20	or/15-19
21	randomized controlled trial/ or random*.ti,ab.
22	20 not 21
23	animal/ not human/
24	nonhuman/
25	exp Animal Experiment/
26	exp Experimental Animal/
27	animal model/
28	exp Rodent/
29	(rat or rats or mouse or mice or rodent*).ti.
30	or/22-29
31	14 not 30
32	limit 31 to english language
33	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
34	32 not 33

2

3 **Database: Cochrane Database of Systematic Reviews Issue 2 of 12, February 2023**

4 **Date of last search: 02/02/2023**

#	Searches
1	MeSH descriptor: [Hyperprolactinemia] this term only
2	MeSH descriptor: [Prolactinoma] this term only
3	(hyperprolactinemi* or hyperprolactinaemi* or HPRL):ti,ab,kw
4	(hypersecret* or (hyper NEXT secret*) or ((inappropriat* or over* or high* or increase* or elevat* or excess* or raised) NEAR/4 (prolactin or PRL or lactotropi* or luteotrop* or LTH or lactogen* or mammatropi* or (milk NEXT hormone*) or (lactat* NEXT hormone*)))):ti,ab,kw

#	Searches
5	(prolactinoma* or microprolactinoma* or macroprolactinoma* or (lactotroph NEXT adenoma*) or (pituitary NEAR/4 (tumor* or tumour* or adenoma* or microadenoma* or macroadenoma* or growth* or neoplasm*))):ti,ab,kw
6	{or #1-#5}
7	MeSH descriptor: [Menstruation Disturbances] this term only
8	MeSH descriptor: [Amenorrhea] this term only
9	MeSH descriptor: [Oligomenorrhea] this term only
10	(amenorrh* or amenia or oligomenorrh*):ti,ab,kw
11	((absen* or stop* or cessation* or cease* or retention* or disorder* or disturb* or issue* or problem* or irregular* or infrequent* or inconsistent* or insufficien* or abnormal* or variation* or variable or dysfunction* or dysregulat* or deviat* or suppress* or miss* or freq* or impair* or lack* or terminat* or decreas* or return* or resum* or restor* or reappear* or regula* or normal*) NEAR/5 (menstrua* or menses or period* or bleed* or catamenia or menarche or cycl* or gonad*)):ti,ab,kw
12	{or #7-#11}
13	#6 AND #12
14	MeSH descriptor: [Dopamine Agonists] this term only
15	MeSH descriptor: [Cabergoline] this term only
16	(cabergolin* or CAB or cabaser or cabaseril or cabarsuss or cabest or dostinex or galastop or actualene or sogilen or sostilar or velactis):ti,ab,kw
17	{or #14-#16}
18	#6 AND #12 AND #17
19	"conference":pt or (clinicaltrials or trialsearch):so
20	#18 NOT #19
21	#20 in Cochrane Reviews, Cochrane Protocols

1

2 **Database: Cochrane Central Register of Controlled Trials Issue 2 of 12, February 2023**

3 **Date of last search: 02/02/2023**

#	Searches
1	MeSH descriptor: [Hyperprolactinemia] this term only
2	MeSH descriptor: [Prolactinoma] this term only
3	(hyperprolactinemi* or hyperprolactinaemi* or HPRL):ti,ab,kw
4	(hypersecret* or (hyper NEXT secret*) or ((inappropriat* or over* or high* or increase* or elevat* or excess* or raised) NEAR/4 (prolactin or PRL or lactotropi* or luteotrop* or LTH or lactogen* or mammatropi* or (milk NEXT hormone*) or (lactat* NEXT hormone*)))):ti,ab,kw
5	(prolactinoma* or microprolactinoma* or macroprolactinoma* or (lactotroph NEXT adenoma*) or (pituitary NEAR/4 (tumor* or tumour* or adenoma* or microadenoma* or macroadenoma* or growth* or neoplasm*))):ti,ab,kw
6	{or #1-#5}
7	MeSH descriptor: [Menstruation Disturbances] this term only
8	MeSH descriptor: [Amenorrhea] this term only
9	MeSH descriptor: [Oligomenorrhea] this term only
10	(amenorrh* or amenia or oligomenorrh*):ti,ab,kw
11	((absen* or stop* or cessation* or cease* or retention* or disorder* or disturb* or issue* or problem* or irregular* or infrequent* or inconsistent* or insufficien* or abnormal* or variation* or variable or dysfunction* or dysregulat* or deviat* or suppress* or miss* or freq* or impair* or lack* or terminat* or decreas* or return* or resum* or restor* or reappear* or regula* or normal*) NEAR/5 (menstrua* or menses or period* or bleed* or catamenia or menarche or cycl* or gonad*)):ti,ab,kw
12	{or #7-#11}
13	#6 AND #12
14	MeSH descriptor: [Dopamine Agonists] this term only
15	MeSH descriptor: [Cabergoline] this term only
16	(cabergolin* or CAB or cabaser or cabaseril or cabarsuss or cabest or dostinex or galastop or actualene or sogilen or sostilar or velactis):ti,ab,kw
17	{or #14-#16}
18	#6 AND #12 AND #17

#	Searches
19	"conference":pt or (clinicaltrials or trialsearch):so
20	#18 NOT #19
21	#20 in Trials

1

2 **Database: Epistemonikos**

3 **Date of last search: 02/02/2023**

#	Searches
1	(hyperprolactinaemi* OR hyperprolactinemi* OR HPRL OR hypersecret* OR (hyper secret*) OR prolactin OR PRL OR lactotropi* OR luteotrop* OR LTH OR lactogen* OR mammatropi* OR (milk hormone*) OR (lactat* hormone*) OR prolactinoma* OR microprolactinoma* OR macroprolactinoma* OR (lactotroph adenoma*) OR (pituitary AND (tumor* OR tumour* OR adenoma* OR microadenoma* OR macroadenoma* OR growth* OR neoplasm*)))
2	(amenorrh* OR amenia OR oligomenorrh* OR (absen* OR stop* OR cessation* OR cease* OR retention* OR disorder* OR disturb* OR issue* OR problem* OR irregular* OR infrequent* OR inconsistent* OR insufficien* OR abnormal* OR variation* OR variable OR dysfunction* OR dysregulat* OR deviat* OR suppress* OR miss* OR freq* OR impair* OR lack* OR terminat* OR decreas* OR return* OR resum* OR restor* OR reappear* OR regula* OR normal*) AND (menstrua* OR menses OR period* OR bleed* OR catamenia OR menarche OR cycl* OR gonad*))
3	(cabergolin* OR CAB OR cabaser OR cabaseril OR cabarsuss OR cabest OR dostinex OR galastop OR actualene OR sogilen OR sostilar OR velactis)
4	1 AND 2 AND 3

4

5 **Health Economic Literature search strategies**

6 **Database: Ovid MEDLINE(R) ALL <1946 to February 02, 2023>**

7 **Date of last search: 03/02/2023**

#	Searches
1	Hyperprolactinemia/ or Prolactinoma/
2	(hyperprolactin?emi* or HPRL).ti,ab,kf.
3	(hypersecret* or hyper secret* or ((inappropriat* or over* or high* or increase* or elevat* or excess* or raised) adj4 (prolactin or PRL or lactotropi* or luteotrop* or LTH or lactogen* or mammatropi* or milk hormone* or lactat* hormone*))).ti,ab,kf.
4	(prolactinoma? or m?croprolactinoma* or lactotroph adenoma? or (pituitary adj4 (tumo?r* or adenoma? or m?croadenoma* or growth* or neoplasm*))).ti,ab,kf.
5	or/1-4
6	menstruation disturbances/ or amenorrhea/ or oligomenorrhea/
7	(amenorrh* or amenia or oligomenorrh*).ti,ab,kf.
8	((absen* or stop* or cessation* or cease* or retention* or disorder* or disturb* or issue* or problem* or irregular* or infrequent* or inconsistent* or insufficien* or abnormal* or variation* or variable or dysfunction* or dysregulat* or deviat* or suppress* or miss* or freq* or impair* or lack* or terminat* or decreas* or return* or resum* or restor* or reappear* or regula* or normal*) adj5 (menstrua* or menses or period* or bleed* or catamenia or menarche or cycl* or gonad*)).ti,ab,kf.
9	or/6-8
10	5 and 9
11	letter/
12	editorial/
13	news/
14	exp historical article/
15	Anecdotes as Topic/
16	comment/
17	case report/
18	(letter or comment*).ti.
19	or/11-18

#	Searches
20	randomized controlled trial/ or random*.ti,ab.
21	19 not 20
22	animals/ not humans/
23	exp Animals, Laboratory/
24	exp Animal Experimentation/
25	exp Models, Animal/
26	exp Rodentia/
27	(rat or rats or mouse or mice or rodent*).ti.
28	or/21-27
29	10 not 28
30	limit 29 to english language
31	Economics/
32	Value of life/
33	exp "Costs and Cost Analysis"/
34	exp Economics, Hospital/
35	exp Economics, Medical/
36	exp Resource Allocation/
37	Economics, Nursing/
38	Economics, Pharmaceutical/
39	exp "Fees and Charges"/
40	exp Budgets/
41	budget*.ti,ab.
42	cost*.ti,ab.
43	(economic* or pharmaco?economic*).ti,ab.
44	(price* or pricing*).ti,ab.
45	(financ* or fee or fees or expenditure* or saving*).ti,ab.
46	(value adj2 (money or monetary)).ti,ab.
47	resourc* allocat*.ti,ab.
48	(fund or funds or funding* or funded).ti,ab.
49	(ration or rations or rationing* or rationed).ti,ab.
50	ec.fs.
51	or/31-50
52	quality-adjusted life years/
53	sickness impact profile/
54	(quality adj2 (wellbeing or well being)).ti,ab.
55	sickness impact profile.ti,ab.
56	disability adjusted life.ti,ab.
57	(qal* or qtime* or qwb* or daly*).ti,ab.
58	(euroqol* or eq5d* or eq 5*).ti,ab.
59	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
60	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
61	(hui or hui1 or hui2 or hui3).ti,ab.
62	(health* year* equivalent* or hye or hyes).ti,ab.
63	discrete choice*.ti,ab.
64	rosser.ti,ab.
65	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
66	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
67	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
68	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
69	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
70	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
71	or/52-70

#	Searches
72	30 and (51 or 71)

1 **Database: Embase <1974 to 2023 February 02>**

2 **Date of last search: 03/02/2023**

#	Searches
1	hyperprolactinemia/ or prolactinoma/
2	(hyperprolactin?emi* or HPRL).ti,ab,kf.
3	(hypersecret* or hyper secret* or ((inappropriat* or over* or high* or increase* or elevat* or excess* or raised) adj4 (prolactin or PRL or lactotropi* or luteotrop* or LTH or lactogen* or mammatropi* or milk hormone* or lactat* hormone*))).ti,ab,kf.
4	(prolactinoma? or m?croprolactinoma* or lactotroph adenoma? or (pituitary adj4 (tumo?r* or adenoma? or m?croadenoma* or growth* or neoplasm*))).ti,ab,kf.
5	or/1-4
6	exp "amenorrhea and oligomenorrhea"/ or menstruation disorder/
7	(amenorrh* or amenia or oligomenorrh*).ti,ab,kf.
8	((absen* or stop* or cessation* or cease* or retention* or disorder* or disturb* or issue* or problem* or irregular* or infrequent* or inconsistent* or insufficien* or abnormal* or variation* or variable or dysfunction* or dysregulat* or deviat* or suppress* or miss* or freq* or impair* or lack* or terminat* or decreas* or return* or resum* or restor* or reappear* or regula* or normal*) adj5 (menstrua* or menses or period* or bleed* or catamenia or menarche or cycl* or gonad*)).ti,ab,kf.
9	or/6-8
10	5 and 9
11	letter.pt. or letter/
12	note.pt.
13	editorial.pt.
14	case report/ or case study/
15	(letter or comment*).ti.
16	or/11-15
17	randomized controlled trial/ or random*.ti,ab.
18	16 not 17
19	animal/ not human/
20	nonhuman/
21	exp Animal Experiment/
22	exp Experimental Animal/
23	animal model/
24	exp Rodent/
25	(rat or rats or mouse or mice or rodent*).ti.
26	or/18-25
27	10 not 26
28	limit 27 to english language
29	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
30	28 not 29
31	health economics/
32	exp economic evaluation/
33	exp health care cost/
34	exp fee/
35	budget/
36	funding/
37	resource allocation/
38	budget*.ti,ab.
39	cost*.ti,ab.
40	(economic* or pharmaco?economic*).ti,ab.
41	(price* or pricing*).ti,ab.

#	Searches
42	(financ* or fee or fees or expenditure* or saving*).ti,ab.
43	(value adj2 (money or monetary)).ti,ab.
44	resourc* allocat*.ti,ab.
45	(fund or funds or funding* or funded).ti,ab.
46	(ration or rations or rationing* or rationed).ti,ab.
47	or/31-46
48	quality adjusted life year/
49	"quality of life index"/
50	short form 12/ or short form 20/ or short form 36/ or short form 8/
51	sickness impact profile/
52	(quality adj2 (wellbeing or well being)).ti,ab.
53	sickness impact profile.ti,ab.
54	disability adjusted life.ti,ab.
55	(qal* or qtime* or qwb* or daly*).ti,ab.
56	(euroqol* or eq5d* or eq 5*).ti,ab.
57	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
58	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
59	(hui or hui1 or hui2 or hui3).ti,ab.
60	(health* year* equivalent* or hye or hyes).ti,ab.
61	discrete choice*.ti,ab.
62	rosser.ti,ab.
63	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
64	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
65	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
66	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
67	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
68	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
69	or/48-68
70	28 and (47 or 69)

1

2 **Database: INAHTA**

3 **Date of last search: 03/02/2023**

#	Searches
1	"Hyperprolactinemia"[mh]
2	"Prolactinoma"[mh]
3	(hyperprolactinaemi* or hyperprolactinemi* or HPRL)
4	(hypersecret* or "hyper secret*" or ((inappropriat* or over* or high* or increase* or elevat* or excess* or raised) AND (prolactin or PRL or lactotropi* or luteotrop* or LTH or lactogen* or mammatropi* or "milk hormone*" or "lactat* hormone*")))
5	((prolactinoma* or microprolactinoma* or macroprolactinoma* or "lactotroph adenoma*" or (pituitary AND (tumor* or tumour* or adenoma* or microadenoma* or macroadenoma* or growth* or neoplasm*)))
6	#5 OR #4 OR #3 OR #2 OR #1
7	"Menstruation Disturbances"[mh]
8	"Amenorrhea"[mh]
9	"Oligomenorrhea"[mh]
10	(amenorrh* or amenia or oligomenorrh*)
11	((absen* or stop* or cessation* or cease* or retention* or disorder* or disturb* or issue* or problem* or irregular* or infrequent* or inconsistent* or insufficien* or abnormal* or variation* or variable or dysfunction* or dysregulat* or deviat* or suppress* or miss* or freq* or impair* or lack* or terminat* or decreas* or return* or resum* or restor* or reappear* or regula* or normal*) AND (menstrua* or menses or period* or bleed* or catamenia or menarche or cycl* or gonad*))
12	#11 OR #10 OR #9 OR #8 OR #7

#	Searches
13	#12 AND #6

Database: HTA via CRD

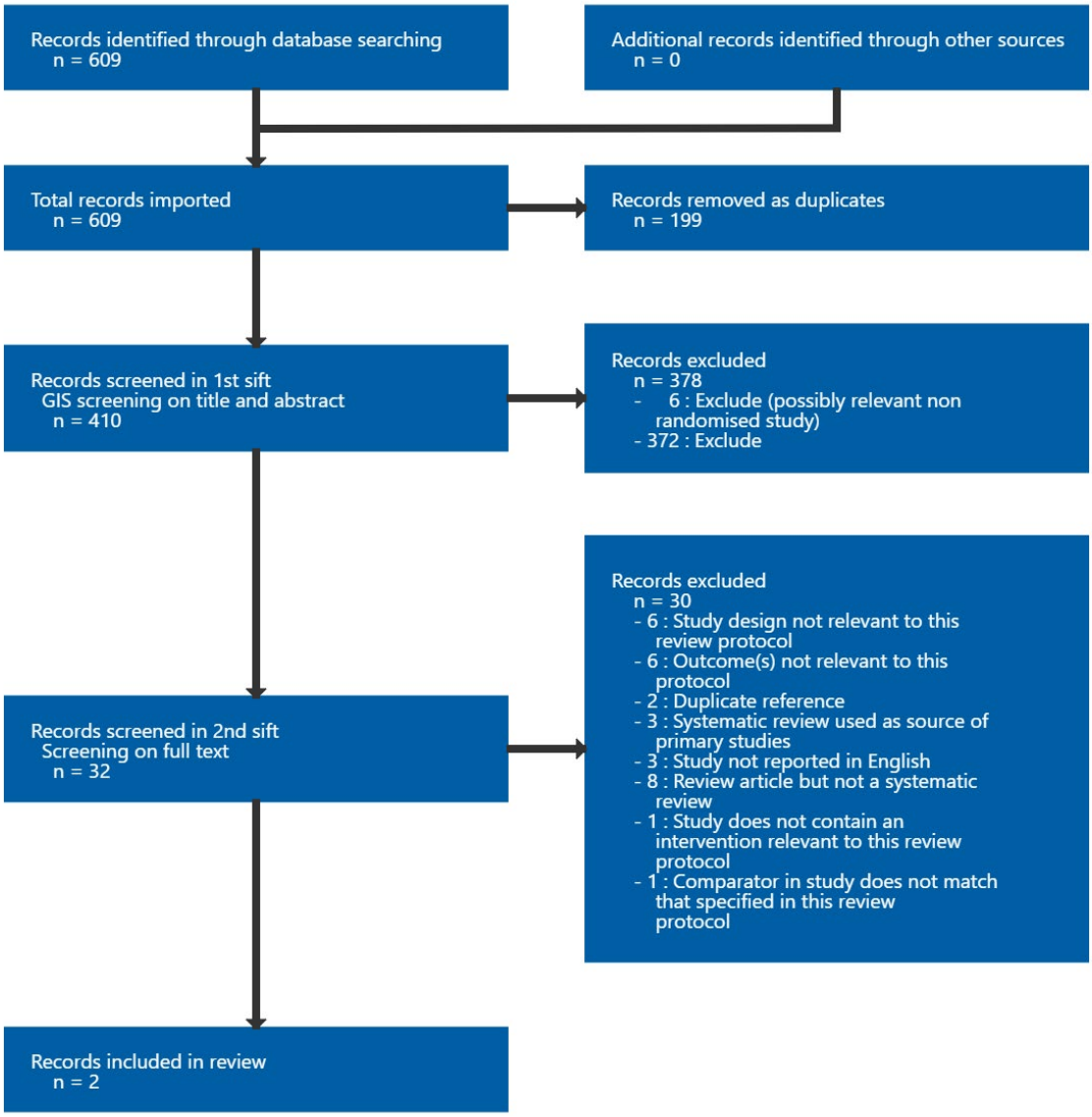
Date of last search: 03/02/2023

#	Searches
1	MeSH DESCRIPTOR Hyperprolactinemia
2	MeSH DESCRIPTOR Prolactinoma
3	((hyperprolactinaemi* or hyperprolactinemi* or HPRL))
4	((hypersecret* or "hyper secret*" or ((inappropriat* or over* or high* or increase* or elevat* or excess* or raised) AND (prolactin or PRL or lactotropi* or luteotrop* or LTH or lactogen* or mammatropi* or "milk hormone*" or "lactat* hormone*"))))
5	((prolactinoma* or microprolactinoma* or macroprolactinoma* or lactotroph adenoma* or (pituitary ADJ4 (tumour* or tumor* or adenoma* or microadenoma* or macroadenoma* or growth* or neoplasm*))))
6	#1 OR #2 OR #3 OR #4 OR #5
7	MeSH DESCRIPTOR menstruation disturbances
8	MeSH DESCRIPTOR amenorrhea
9	MeSH DESCRIPTOR oligomenorrhea
10	((amenorrh* or amenia or oligomenorrh*))
11	(((absen* or stop* or cessation* or cease* or retention* or disorder* or disturb* or issue* or problem* or irregular* or infrequent* or inconsistent* or insufficien* or abnormal* or variation* or variable or dysfunction* or dysregulat* or deviat* or suppress* or miss* or freq* or impair* or lack* or terminat* or decreas* or return* or resum* or restor* or reappear* or regula* or normal*) ADJ5 (menstrua* or menses or period* or bleed* or catamenia or menarche or cycl* or gonad*)))
12	#7 OR #8 OR #9 OR #10 OR #11
13	#6 AND #12
14	(#6 AND #12) IN HTA

Appendix C Effectiveness evidence study selection

Study selection for: What is the clinical and cost effectiveness of cabergoline for fertility problems associated with hyperprolactinaemic amenorrhoea or oligomenorrhea?

Figure 1: Study selection flow chart



Appendix D Evidence tables

Evidence tables for review question: What is the clinical and cost effectiveness of cabergoline for fertility problems associated with hyperprolactinaemic amenorrhoea or oligomenorrhea?

Motazedian, 2010

Bibliographic Reference	Motazedian, Shahdokht; Babakhani, Lida; Fereshtehnejad, Seyed-Mohammad; Mojthahedi, Khatereh; A comparison of bromocriptine & cabergoline on fertility outcome of hyperprolactinemic infertile women undergoing intrauterine insemination.; The Indian journal of medical research; 2010; vol. 131; 670-4

Study details

Country where study was carried out	Iran
Study type	Randomised controlled trial (RCT)
Study dates	March 2005 to March 2007
Inclusion criteria	Primary or secondary infertility; Hyperprolactinemia with or without galactorrhoea (prolactin > 20 ng/ml); and normal HA except high prolactin level, normal HSG or laparoscopy and normal SA.
Exclusion criteria	Patients with other causes of infertility such as tubal factor, male factor and unexplained infertility; women with nausea, vomiting, orthostatic hypotension, chronic hypertension, headache, sensitivity to ergot derivatives, macroadenoma of pituitary gland and previous use of bromocriptine or cabergoline without effect.
Patient characteristics	**Age, years: mean (SD)** Cabergoline: 29.17 (4.47); range 20-37 Bromocriptine: 28.62 (4.42); range 19-38 **Duration of infertility, years: mean (SD)** Cabergoline: 4.48 (2.06); range 2-10

	Bromocriptine: 4.52 (1.71); range 2-10 **Serum level of prolactin, (ng/ml): mean (SD)** Cabergoline: 65.31 (16.07); range 34-105 Bromocriptine: 64.02 (18.64); range 22-105 **Irregular menstruation: number (%)** Cabergoline: 81 (91) Bromocriptine: 84 (89.4)
Intervention(s)/control	Intervention: Cabergoline 0.25mg twice per week Control: Bromocriptine 2.5mg twice per day Induction of ovulation was started when prolactin levels became normal, and if they did not become normal, the paritipant was excluded from the study. Clomifene citrate was administrated orally for 5 d with the dose of 100 mg/d from the 5th to the 9th day of cycle, and HMG (Merionol, IBSA, Switzerland) was injected intramuscularly with 2 Amp/d from the 8th day of cycle. Vaginal sonography was performed on the day 10th or 11th of cycle and according to the size and number of stimulated follicles, HMG was continued till at least 2 dominant follicles with size of >18 mm were seen. If this condition was not achieved, HMG was discontinued and restarted from the next cycle. In addition, there was no cancellation due to hyperstimulation or excessive number of follicles. Then 5000-10000 IU HCG (Choriomon, IBSA, Switzerland) was injected intramuscularly. IUI was performed 24-36 h after swim-up method.
Duration of follow-up	Unclear; pregnancy was documented by transvaginal sonography, at 6-7 weeks of gestational age.
Sources of funding	Research deputy of Shiraz University of Medical Sciences
Sample size	N=183
Other information	Study includes hyperprolactinaemic infertile women undergoing induction of ovulation for IUI

1

Study arms

Cabergoline (N = 89)

Bromocriptine (N = 94)

Outcomes

Outcome	Cabergoline, N = 89	Bromocriptine, N = 94
Pregnancy Documented by transvaginal sonography, at 6-7 weeks of gestational age. No of events	n = 73; % = 82	n = 53; % = 56.4

Pregnancy - Polarity - Higher values are better

Critical appraisal

Critical appraisal – Cochrane RoB 2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns due to a lack of allocation concealment.
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns due to participants and personnel likely aware of the intervention and an absence of reporting on any deviations from the intended interventions.
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns due to the timing of outcome assessment (at 6-7 weeks of gestational age).

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns (Unclear whether there was allocation concealment and whether deviations arose because of the trial context, and participants and intervention administrators appeared to be aware of the assigned intervention. There were also concerns about the timing of the outcome assessment (at 6-7 weeks of gestational age)
Overall bias and Directness	Overall Directness	Indirectly applicable (the administration clomifene citrate and human menopausal gonadotropin to participants for ovulation induction is not usual practice)
Overall bias and Directness	Risk of bias variation across outcomes	None

Webster, 1994

Bibliographic Reference	Webster, J; Piscitelli, G; Polli, A; Ferrari, C I; Ismail, I; Scanlon, M F; A comparison of cabergoline and bromocriptine in the treatment of hyperprolactinemic amenorrhea. Cabergoline Comparative Study Group.; The New England journal of medicine; 1994; vol. 331 (no. 14); 904-9

Study details

Countries where study was carried out	Europe and Argentina
Study type	Randomised controlled trial (RCT)
Study dates	Not reported
Inclusion criteria	Women between 16 - 45 years of age, who had amenorrhea for at least 3 months, and serum prolactin concentrations at least twice the upper limit of normal values for each centre on 2 occasions at least 4 weeks after discontinuation of any previous therapy.

	Women treated previously with either drug were included unless they had discontinued treatment because of adverse events or did not have a 50% reduction in serum prolactin concentrations.
Exclusion criteria	Presence of pituitary macroadenoma, any disorder that could prevent normal menstruation after the restoration of normoprolactinemia, hyperprolactinemia related to polycystic ovary disease, thyroid or adrenal disorders, renal or hepatic disease, and a history of allergy to ergot derivatives.
Patient characteristics	**Age, years: mean (SD)** Bromocriptine: 31 (7) Cabergoline: 31(7) **Diagnosis: no. events** **Microprolactinoma** Bromocriptine: 139 Cabergoline: 140 **Idiopathic hyperprolactinemia** Bromocriptine: 88 Cabergoline: 79 **Empty sella** Bromocriptine: 7 Cabergoline: 2 **Other**

	Bromocriptine: 2 Cabergoline: 2 **Baseline serum prolactin (ug/litre): mean (SD)** Bromocriptine: 118 (124) Cabergoline: 117 (99) **Duration of amenorrhea (months): mean (SD)** Bromocriptine: 18 (30) Cabergoline: 16 (26)
Intervention(s)/control	Intervention: Cabergoline (0.5 to 1.0mg twice weekly): Initially participants received 0.25mg on days 1 and 5 (evening doses), and doses were increased to 0.5mg on the same days during weeks 2 to 8. Dose adjustments were made at the end of week 8 or week 16 based on the serum prolactin values. Doses for Cabergoline were increased to 0.5mg 3 times weekly (days 1, 3 and 5) and then to 1mg weekly. Control: Bromocriptine (2.5 to 5.0mg twice daily): Initially participants received 1.25mg on days 1 to 3 (evening doses), and the dose was increased to 2.5mg daily on days 4 to 7, and subsequently to 2.5mg daily during weeks 2 to 8. Dose adjustments were made at the end of week 8 or week 16 based on the serum prolactin values. Doses for Bromocriptine were increased from 2.5mg twice daily to 2.5mg 3 times daily and subsequently to 5mg twice daily. Intervention and control lasted for 24 weeks (8 weeks double blinded and 16 weeks open)
Duration of follow-up	24 weeks
Sources of funding	Supported by Farmitalia Carlo Erba
Sample size	N=459
Other information	At baseline, 434 of the 459 women had amenorrhea; 14 women in the Bromocriptine group and 11 in the Cabergoline group reported vaginal bleeding in the preceding three months.

	During the double-blind period (weeks 1-8), participants at risk of becoming pregnant were advised to use barrier contraception, but in the open label period (weeks 9-24) only those taking cabergoline were advised to continue such measures. Treatment was stopped if pregnancy was confirmed. There was n=12 pregnancies in the Bromocriptine group and n=18 pregnancies in the Cabergoline group. N=16 participants treated with bromocriptine and 25 treated with cabergoline conceived, but only pregnancies in the latter group were actively monitored. There were 4 elective terminations because of unintended pregnancy, 2 early spontaneous abortions, 16 deliveries (1 caesarean and 15 vaginal) and 1 therapeutic abortion in one participant carrying an abnormal fetus (the fetus had anomalies of the legs probably related to amniotic bands); 2 participants were lost to follow-up. All infants delivered were normal.

Study arms

Cabergoline (N = 223)

Bromocriptine (N = 236)

Outcomes

Study timepoints

- Baseline
- 24 weeks (Endpoint)

Outcomes

Outcome	Cabergoline, 24-week, N=221	Bromocriptine, 24-week, N=231
Clinical efficacy complete success (Percentages are based on numbers randomised, Cabergoline=223, Bromocriptine=236) Occurrence of at least two consecutive menses with biochemical evidence of ovulation on at least one occasion (plasma progesterone concentration above 7.9ng/mL [25nmol/L] in midluteal	n = 161; % = 72	n = 123; % = 52

Outcome	Cabergoline, 24-week, N=221	Bromocriptine, 24-week, N=231
phase or above 3.2ng/mL [10nmol/L] not during midluteal phase) or pregnancy No of events		
At least one ovulatory cycle (Percentages are based on Cabergoline n=191, Bromocriptine n=187) In women whose menses resumed, and plasma progesterone was measured at least once No of events	n = 156; % = 82	n = 123; % = 66

Clinical efficacy complete success - Polarity - Higher values are better
At least one ovulatory cycle - Polarity - Higher values are better
The number of completers for 24 weeks treatment are Cabergoline=186 and Bromocriptine=169

Critical appraisal

Critical appraisal – Cochrane RoB 2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns as participants, carers or people delivering the interventions were aware of intervention groups during the trial and deviations from intended interventions likely arose because of the trial context where treatment was stopped if a pregnancy was confirmed. These deviations were mostly balanced between the intervention groups (n=12 bromocriptine group, n=18 cabergoline group) however as part of the trial context only women in the cabergoline group were advised to use barrier contraception in weeks 9-24.
Domain 2b: Risk of bias due to deviations from the intended	Risk of bias judgement for deviations from the intended	Low

Section	Question	Answer
interventions (effect of adhering to intervention)	interventions (effect of adhering to intervention)	
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns as there is no information on whether the result being assessed is likely to have been selected, on the basis of the results, from multiple eligible analyses of the data. It is unclear why ovulation rate was reported only amongst women whose menses had returned and where plasma progesterone was measured at least once.
Overall bias and Directness	Risk of bias judgement	Some concerns (The study was double blinded during weeks 1-8, but open label between weeks 9-24. Women at risk of becoming pregnant were advised to use barrier contraception during the double-blind period, but in the open label period, only participants taking Cabergoline were advised to continue such measures. Ovulation rate data was reported only amongst women whose menses had returned and where plasma progesterone was measured at least once.)
Overall bias and Directness	Overall Directness	Indirectly applicable (lack of clarity as to whether participants had a health-related fertility problem)
Overall bias and Directness	Risk of bias variation across outcomes	None

Appendix E Forest plots

Forest plots for review question: What is the clinical and cost effectiveness of cabergoline for fertility problems associated with hyperprolactinaemic amenorrhoea or oligomenorrhea?

No meta-analysis was conducted for this review question and so there are no forest plots.

Appendix F GRADE tables

GRADE tables for review question: What is the clinical and cost effectiveness of cabergoline for fertility problems associated with hyperprolactinaemic amenorrhoea or oligomenorrhea?

Table 4: Evidence profile for comparison between Cabergoline and Bromocriptine

Quality assessment							No of participants		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cabergoline	Bromocriptine	Relative (95% CI)	Absolute		
Pregnancy as documented by transvaginal sonography at 6-7 weeks of gestational age; better indicated by higher values)												
1 (Motazedian 2010)	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	73/89 (82%)	53/94 (56.4%)	RR 1.45 (1.19 to 1.78)	254 more per 1000 (from 107 more to 440 more)	VERY LOW	CRITICAL
Complete clinical success as measured by the occurrence of at least two consecutive menses with biochemical evidence of ovulation on at least one occasion or pregnancy at 24-weeks; better indicated by higher values)												
1 (Webster 1994)	randomised trials	serious[1]	no serious inconsistency	serious[4]	serious[3]	none	72/223 (32.3%)	52/236 (22%)	RR 1.47 (1.08 to 1.99)	104 more per 1000 (from 18 more to 218 more)	VERY LOW	IMPORTANT
At least one ovulatory cycle in women whose menses resumed and plasma progesterone was measured at least once at 24-weeks; better indicted by higher values)												
1 (Webster 1994)	randomised trials	serious[1]	no serious inconsistency	serious[4]	serious[3]	none	156/191 (81.7%)	123/187 (65.8%)	RR 1.24 (1.10 to 1.40)	158 more per 1000 (from 66 more to 263 more)	VERY LOW	IMPORTANT

CI: confidence interval; RR: relative risk

[1]Serious risk of bias in the evidence contributing to the outcomes as per RoB 2

[2] Intervention is indirect due to the administration of clomifene citrate and human menopausal gonadotropin to participants for ovulation induction, which is not usual practice,

[3] 95% CI crosses 1 MID (1.25)

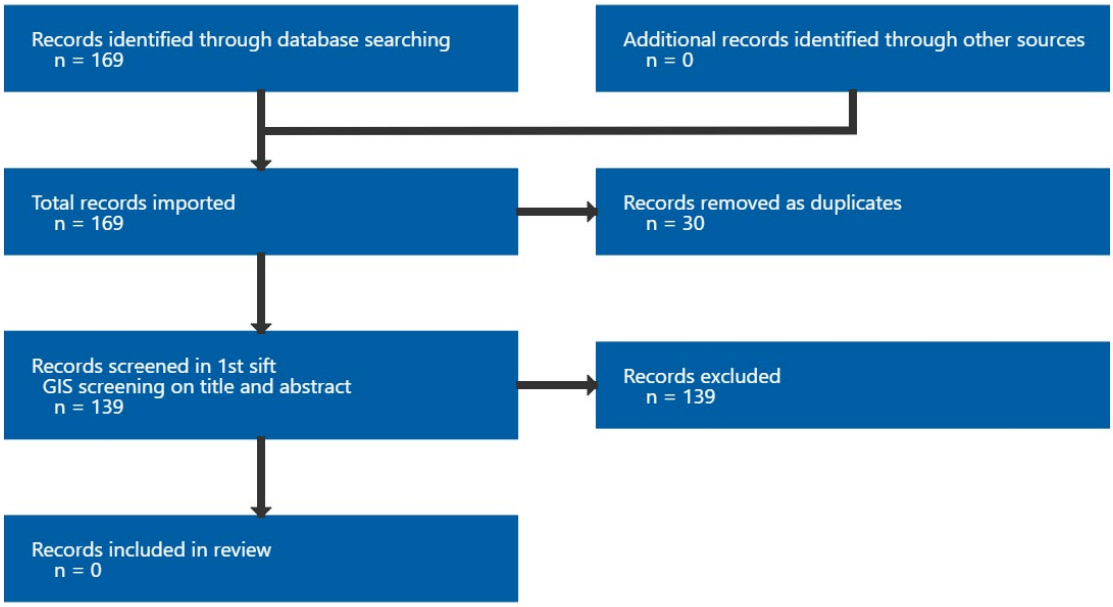
[4] Population is indirect due to lack of clarity as to whether participants had a health-related fertility problem

Appendix G Economic evidence study selection

Study selection for: What is the clinical and cost effectiveness of cabergoline for fertility problems associated with hyperprolactinaemic amenorrhoea or oligomenorrhea?

No economic evidence was identified which was applicable to this review question.

Figure 2: Study selection flow chart



Appendix H Economic evidence tables

Economic evidence tables for review question: What is the clinical and cost effectiveness of cabergoline for fertility problems associated with hyperprolactinaemic amenorrhoea or oligomenorrhea?

No evidence was identified which was applicable to this review question.

Appendix I Economic model

Economic model for review question: What is the clinical and cost effectiveness of cabergoline for fertility problems associated with hyperprolactinaemic amenorrhoea or oligomenorrhea?

No economic analysis was conducted for this review question.

Appendix J Excluded studies

Excluded studies for review question: What is the clinical and cost effectiveness of cabergoline for fertility problems associated with hyperprolactinaemic amenorrhoea or oligomenorrhea?

Excluded effectiveness studies

Table 5: Excluded studies and reasons for their exclusion

Study	Reason for exclusion
Alhusaynei, AJ; Mahmood, IH; Sattam, Z (2007) Comparison of the effects of cabergoline and bromocriptine in women with hyperprolactinemic amenorrhea. Pak j med health sci 1(1): 24-27	- Outcome(s) not relevant to this protocol
Anonymous (2000) Cabergoline and hyperprolactinaemia: new preparation. Better than bromocriptine. Prescrire international 9(45): 195-7	- Review article but not a systematic review
Biller, B M, Luciano, A, Crosignani, P G et al. (1999) Guidelines for the diagnosis and treatment of hyperprolactinemia. The Journal of reproductive medicine 44(12suppl): 1075-84	- Review article but not a systematic review
Brownell, J. (1998) Quinagolide in hyperprolactinaemia. Reviews in Contemporary Pharmacotherapy 9(1): 1-75	- Review article but not a systematic review
Chen, Hengxi; Fu, Jing; Huang, Wei (2016) Dopamine agonists for preventing future miscarriage in women with idiopathic hyperprolactinemia and recurrent miscarriage history. The Cochrane database of systematic reviews 7: cd008883	- Study does not contain an intervention relevant to this review protocol: Bromocriptine versus no treatment
Ciccarelli, E, Giusti, M, Miola, C et al. (1989) Effectiveness and tolerability of long term treatment with cabergoline, a new long-lasting ergoline derivative, in hyperprolactinemic patients. The Journal of clinical endocrinology and metabolism 69(4): 725-8	- Comparator in study does not match that specified in this review protocol
De Luis, D A, Becerra, A, Lahera, M et al. (2000) A randomized cross-over study comparing cabergoline and quinagolide in the treatment of hyperprolactinemic patients. Journal of endocrinological investigation 23(7): 428-34	- Outcome(s) not relevant to this protocol
Di Sarno, A, Landi, ML, Marzullo, P et al. (2000) The effect of quinagolide and cabergoline, two selective dopamine receptor type 2 agonists, in the treatment of prolactinomas. Clinical endocrinology 53(1): 53-60	- Study design not relevant to this review protocol: non-randomised study
dos Santos Nunes, Vania, El Dib, Regina, Boguszewski, Cesar Luiz et al. (2011) Cabergoline versus bromocriptine in the treatment of hyperprolactinemia: a systematic review of randomized controlled trials and meta-analysis. Pituitary 14(3): 259-65	- Systematic review cannot be included as it does not meta analyse outcomes of interest; used as source of primary studies

Study	Reason for exclusion
Fachi, Mariana Millan, de Deus Bueno, Lays, de Oliveira, Denise Colaco et al. (2021) Efficacy and safety in the treatment of hyperprolactinemia: A systematic review and network meta-analysis. Journal of clinical pharmacy and therapeutics 46(6): 1549-1556	- Outcome(s) not relevant to this protocol
Ferrari, C, Mattei, A, Melis, G B et al. (1989) Cabergoline: long-acting oral treatment of hyperprolactinemic disorders. The Journal of clinical endocrinology and metabolism 68(6): 1201-6	- Study design not relevant to this review protocol
Ferrari, C, Paracchi, A, Mattei, A M et al. (1992) Cabergoline in the long-term therapy of hyperprolactinemic disorders. Acta endocrinologica 126(6): 489-94	- Study design not relevant to this review protocol: non-randomised study
Ferrari, C; Piscitelli, G; Crosignani, P G (1995) Cabergoline: a new drug for the treatment of hyperprolactinaemia. Human reproduction (Oxford, England) 10(7): 1647-52	- Review article but not a systematic review
Fideleff, HL, Holland, ME, Chervin, A et al. (1997) Treatment of hyperprolactinemic amenorrhea with cabergoline. Medicina 57(6): 657-661	- Study not reported in English
Fideleff, HL, Holland, ME, Chervin, A et al. (1997) Treatment of hyperprolactinemic amenorrheas with cabergoline. TRATAMIENTO DE AMENORREAS HIPERPROLACTINEMICAS CON CABERGOLINA. Medicina 57(6): 657-661	- Duplicate reference: study not reported in English
Giusti, M, Porcella, E, Carraro, A et al. (1994) A cross-over study with the two novel dopaminergic drugs cabergoline and quinagolide in hyperprolactinemic patients. Journal of endocrinological investigation 17(1): 51-7	- Study design not relevant to this review protocol: crossover randomised controlled trial
Heath, V. (2010) Reproductive endocrinology: High-dose cabergoline improves pregnancy rates in women with prolactinomas. Nature Reviews Endocrinology 6(8): 415	- Study design not relevant to this review protocol: review article of a non-randomised study
Jackson, J. and Safranek, S. (2005) What is the recommended evaluation and treatment for elevated serum prolactin?. Journal of Family Practice 54(10): 897	- Review article but not a systematic review
Mahmood, I.H.; Al-Husaynei, A.J.; Mohamad, S.H. (2010) Comparative effects of bromocriptine and cabergoline on serum prolactin levels, liver and kidney function tests in hyperprolactinemic women. Pakistan Journal of Medical Sciences 26(2): 255-260	- Study design not relevant to this review protocol: non-randomised study
Mattei, A M, Ferrari, C, Baroldi, P et al. (1988) Prolactin-lowering effect of acute and once weekly repetitive oral administration of cabergoline at two dose levels in hyperprolactinemic patients. The Journal of clinical endocrinology and metabolism 66(1): 193-8	- Outcome(s) not relevant to this protocol

Study	Reason for exclusion
Paoletti, AM, Cagnacci, A, Depau, GF et al. (1996) The chronic administration of cabergoline normalizes androgen secretion and improves menstrual cyclicity in women with polycystic ovary syndrome. Fertility and sterility 66(4): 527-32	- Outcome(s) not relevant to this protocol
Pascal-Vigneron, V, Weryha, G, Bosc, M et al. (1995) Cabergoline versus bromocriptine for hyperprolactinaemic amenorrhea. Results of a multicentric, randomized, double-blind trial in France. AMENORRHEE HYPERPROLACTINEMIQUE: TRAITEMENT PAR CABERGOLINE VERSUS BOMOCRIPTINE. RESULTATS DE L'ETUDE NATIONALE, MULTICENTRIQUE, RANDOMISEE, EN DOUBLE INSU. Presse medicale 24(16): 753-757	- Duplicate reference: study not reported in English
Pascal-Vigneron, V, Weryha, G, Bosc, M et al. (1995) Hyperprolactinemic amenorrhea: treatment with cabergoline versus bromocriptine. Results of a national multicenter randomized double-blind study. Presse medicale (Paris, France : 1983) 24(16): 753-757	- Study not reported in English
Rains, C P; Bryson, H M; Fitton, A (1995) Cabergoline. A review of its pharmacological properties and therapeutic potential in the treatment of hyperprolactinaemia and inhibition of lactation. Drugs 49(2): 255-79	- Review article but not a systematic review
Triantafilo, Nicolas; Castro-Gutierrez, Victoria; Rada, Gabriel (2016) Cabergoline or bromocriptine for prolactinoma?. Medwave 16(suppl3): e6545	- Systematic review cannot be included due to poor quality and the inclusion of non-randomised studies; used as source of primary studies
Wang, Amy T, Mullan, Rebecca J, Lane, Melanie A et al. (2012) Treatment of hyperprolactinemia: a systematic review and meta-analysis. Systematic reviews 1: 33	- Systematic review cannot be included due to the inclusion of non-randomised studies; used as source of primary studies
Watanabe, S, Takano, S, Akutsu, H et al. (2011) [Prolactinoma treatment status in the cabergoline era]. No shinkei geka. Neurological surgery 39(11): 1045-54	- Study not reported in English
Webster, J (1996) A comparative review of the tolerability profiles of dopamine agonists in the treatment of hyperprolactinaemia and inhibition of lactation. Drug safety 14(4): 228-38	- Review article but not a systematic review
Webster, J (1999) Dopamine agonist therapy in hyperprolactinemia. The Journal of reproductive medicine 44(12suppl): 1105-10	- Review article but not a systematic review
Webster, J, Piscitelli, G, Polli, A et al. (1992) Dose-dependent suppression of serum prolactin by cabergoline in hyperprolactinaemia: a placebo controlled, double blind, multicentre study. European Multicentre Cabergoline Dose-finding Study Group. Clinical endocrinology 37(6): 534-41	- Outcome(s) not relevant to this protocol

1

Excluded economic studies

No economic evidence was identified for this review.

Appendix K Research recommendations – full details

Research recommendations for review question: What is the clinical and cost effectiveness of cabergoline for fertility problems associated with hyperprolactinaemic amenorrhoea or oligomenorrhea?

No research recommendations were made for this review question.