ORIGINAL ARTICLE: ASSISTED REPRODUCTION

Cabergoline for the prevention of ovarian hyperstimulation syndrome: systematic review and meta-analysis of randomized controlled trials

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Objective: To evaluate the efficacy and safety of using cabergoline for reducing the risk of ovarian hyperstimulation syndrome (OHSS).
Design: Systematic review and meta-analysis of randomized clinical trials (RCTs).
Patients: Women submitted to controlled ovarian stimulation (COS) for assisted reproduction.
Interventions: Cabergoline.
Setting: Fertility centers.
Main outcome measures: Moderate-severe OHSS, live birth, clinical pregnancy, number of retrieved oocytes, miscarriage, congenital abnormalities. Comparisons were performed with the use of risk ratios (RRs) or mean differences (MDs) and their respective 95% confidence intervals (CIs).
Result(s): Eight RCTs were considered to be eligible; data from seven studies could be extracted and included in the meta-analysis. Cabergoline reduces the risk of moderate-severe OHSS (RR 0.38, 95% CI 0.29–0.51, 7 studies, 858 women) and probably has no clinically relevant negative impact on clinical pregnancy (RR 1.02, 95% CI 0.78–1.34, 4 studies, 561 women) or on the number of retrieved oocytes (MD 1.15, 95% CI −0.76 to 3.07, 5 studies, 628 women). However, our estimates were imprecise for distinguishing between substantial harm, no effect, and substantial benefit considering live birth (RR 1.03, 95% CI 0.71–1.48, 1 study, 200 women), and miscarriage (RR 0.69, 95% CI 0.27 to 1.76, 3 studies, 194 pregnant women). No studies reported congenital abnormalities.
Conclusion(s): Cabergoline reduces the occurrence of moderate-severe OHSS. Cabergoline is unlikely to have a clinically relevant negative impact on clinical pregnancy or on the number of retrieved oocytes. However, we are still uncertain of its impact on live birth, miscarriage, and congenital abnormalities. (Fertil Steril® 2013;■:■–■. ©2013 by American Society for Reproductive Medicine.)
Key Words: Cabergoline, ovarian hyperstimulation syndrome, assisted reproductive techniques, ovulation induction, review

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Subfertility is defined as not being able to conceive after 1 year, which means being less fertile than a typical couple (1). Subfertility is a very common condition, affecting ~15% of the women at reproductive age (2, 3), and assisted reproductive techniques (ART)—i.e., interventions that require the in vitro handling of both human oocytes and sperm or of embryos, with the objective of achieving pregnancy and live birth (4)—are widely used in this condition. Controlled ovarian stimulation (COS) is considered to be an important part of ART: The pregnancy rate per cycle is ~10% when minimal or no COS is performed (5, 6), and achieves 33% when standard COS is performed (7). However, COS imposes the risk of ovarian hyperstimulation syndrome (OHSS), a potentially life-threating condition (8).

Several interventions have been introduced to decrease the risk of moderate and severe OHSS, namely, cycle cancellation (9), coasting (10),

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cryopreservation of all embryos (11), albumin (12), replacing FSH with low-dose hCG (13), cabergoline (14), and replacing hCG with a GnRH agonist to induce final follicular maturation (15, 16). This latter intervention seems to be the most effective in reducing OHSS, but it is associated with a reduced chance of implantation (17) and can not be used in women who received GnRH agonists for pituitary suppression in the same COS cycle. Cabergoline is probably not as effective for decreasing the incidence of OHSS, but it can be used by all women undergoing COS at high risk of OHSS, and there is no evidence of decreased implantation rates (18). The rationale for using cabergoline is that it might counteract the increased production of vascular endothelial growth factor (VEGF) by the follicles after hCG administration, which is thought to be the specific key process leading to the development of OHSS (8). It has been demonstrated in an animal model that cabergoline, a dopamine agonist, partially inhibits the ovarian VEGF receptor 2 (VEGFR-2) through a decrease in its phosphorylation levels (19); such inhibition, in turn, decreases the VEGFR-2–induced vascular permeability, without affecting luteal angiogenesis. This finding sparked interest in cabergoline as a potential intervention for preventing OHSS, and a clinical trial evaluating the efficacy of cabergoline in this setting was published a couple of years later (20). Although a systematic review on this topic was already published not long ago (18), it included only two studies (14, 20), and there are several other randomized controlled trials (RCTs) on this subject (21–26).

Our objective was to evaluate the effectiveness and safety of using cabergoline for reducing the risk of OHSS in women undergoing COS for ART by performing a systematic review and meta-analysis of the existing RCTs.

METHODS

Protocol and Registration

The protocol for this review was registered at PROSPERO (CRD42013004259).

Eligibility Criteria

Studies. Only truly randomized controlled trials (RCTs) were considered to be eligible; quasi- or pseudorandomized trials were not included. Cross-over trials were included only if data regarding the first treatment of each participant were available.

Participants. The included RCTs studied women undergoing COS for ART.

Interventions. The included RCTs studied cabergoline (alone or combined with other intervention) vs. placebo, no treatment, or other treatment for reducing the risk of OHSS.

Information Sources

We searched for RCTs in the following electronic databases from their inception: Cochrane Central Register of Controlled Trials (CENTRAL), Cumulative Index to Nursing and Allied Health Literature (CINAHL; www.ebscohost.com/cinahl/), Embase, Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS), Medical Literature Analysis and Retrieval System Online (MEDLINE), and PsycINFO. We searched for study protocols and ongoing trials in the following trial registries: ClinicalTrials.gov (www.clinicaltrials.gov), Current Controlled Trials (www.controlled-trials.com/isrctn/), and World Health Organization International Trials Registry Platform search portal (www.who.int/trialsearch/Default.aspx). We searched for gray literature in Open Grey (www.opengrey.eu).

Search

The following terms were used, adjusting for each database as necessary: ((cabergoline) OR (ergoline) OR (dopamine agonist)) AND ((in vitro fertilization*) OR (in vitro fertilisation*) OR (IVF) OR (test-tube) OR (Intracytoplasmic Sperm Injection*) OR (ICSI) OR (reproduct*) OR (embryo transfer) OR (blastocyst transfer)) AND ((trial) OR (random*)). Additionally, we hand-searched the reference lists from included trials and similar reviews.

Study Selection

Titles and abstracts were reviewed independently by two review authors (L.M.D.S. and V.M.S.L.), who checked for duplicates and applied the pre-established criteria for inclusion. The same review authors further evaluated the eligibility of potentially eligible records; disagreements were solved by consulting another review author (W.P.M.). Authors tried to correspond with study investigators to clarify study eligibility when required. Searches were not limited by language, publication date, or publication status.

Data Collection Process

We extracted data from included trials with the use of a data extraction form designed and pilot tested by the authors. When trials had multiple publications, the main trial report was used as reference and additional details were supplemented from secondary papers. We tried to correspond with study investigators to solve any query as required. Data were extracted independently, in a standardized manner, by two review authors (L.M.D.S. and V.M.S.L.), and were checked by a third (R.M.M.). Disagreements were solved by consulting another author (W.P.M.).

Data Items

Study characteristics. Authors, country, institution, funding sources, conflicts of interest, informed consent, ethical approval, study design, period of enrollment, inclusion criteria, exclusion criteria, number of participants in each group at each stage, age and body mass index (BMI; mean ± SD) of participants in each group, proportion of IVF/intracytoplasmic sperm injection (ICSI) in each group.

Primary outcomes. OHSS per randomized woman.

Secondary outcomes. Live birth per randomized woman (birth of twins/triplets counted as a single live birth), Clinical pregnancy per randomized woman, number of oocytes

retrieved (mature, preferentially, or total number) per randomized woman, miscarriage per clinical pregnancy, congenital abnormality per clinical pregnancy.

Dealing with missing data. We tried to contact the study authors to obtain missing data. When they were unobtainable, we assumed that clinical pregnancy (and subsequent miscarriage or live birth) did not occur and that no oocyte was retrieved from women with cycle cancellation to perform an intention-to-treat (ITT) analysis. However, when some of the participants were excluded from analysis by other causes, we did not perform an ITT analysis, because we could not make any safe assumption, and these studies were judged to be at a high risk of attrition bias.

Implantation and cleavage rates were included only for completeness in the "Characteristics of included studies" tables.

Risk of Bias in Individual Studies

Two of the authors (R.M.M. and W.P.M.) independently assessed the risk of selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessors), attrition bias (incomplete outcome data), reporting bias (selective outcome reporting), and other potential sources of bias (e.g., difference in the number of embryos transferred, age of participants, co-interventions, early stopping). Disagreements were solved by consulting another author (C.O.N.). To judge the risk of bias, we followed The Cochrane Collaboration's criteria for judging risk of bias (27): The trials were classified as being of "low," "high," or "unclear" risk of bias.

Summary Measures

The effects of the interventions were summarized as risk ratios (RRs) or as Peto odds ratios (ORs) for binary outcomes (OHSS, live birth, clinical pregnancy, miscarriage, congenital abnormality) and as mean differences (MDs) for continuous outcomes (number of oocytes retrieved). Regarding the binary outcomes, we preferred to use RR because it is easier to interpret: Misinterpretation of the OR as if it was equal to the RR tends to overestimate the intervention effect, especially when events are common. There is concern that this misinterpretation occurs frequently in published reports of individual studies and systematic reviews (27). However, we had planned to use Peto OR if there was a zero cell count or if the prevalence of the event was $<1\%$ (at least in one group), because in these situations Peto OR is considered to be the least biased and most powerful measure, providing the best confidence interval coverage (27), and the resulting OR value is very similar to the RR, thus avoiding misinterpretations. The precision of the estimates was evaluated by the 95% confidence interval (CI). We considered the clinical relevance of all comparisons, taking into account the precision of the estimates; we determined the number needed to treat for an additional beneficial outcome (NNTB) or an additional harmful outcome (NNTH) when a significant difference was observed in the binary outcomes.

Synthesis of Results

All results were combined for meta-analysis with the use of Review Manager 5.1 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2011). Heterogeneity was assessed by the I^2 statistic. The data from primary studies were combined comparing cabergoline (alone or combined with another intervention) vs. no intervention or a different intervention. An increase in the risk of a particular outcome associated with cabergoline, which may be beneficial (e.g., live birth) or detrimental (e.g., OHSS), was displayed graphically in the forest plots to the right of the center line and a decrease in the risk of an outcome to the left of the center line.

Because the included studies used different comparators with cabergoline, we stratified the results, separating the studies by the interventions used to reduce the risk of OHSS: 1) cabergoline vs. no treatment or placebo; 2) cabergoline + albumin vs. albumin; 3) cabergoline + hydroxyethyl starch (HES) vs. HES; 4) cabergoline vs. prednisolone or no treatment; 5) cabergoline vs. albumin; and 6) cabergoline vs. coasting.

Risk of Bias across Studies

In view of the difficulty in detecting and correcting for publication bias and other reporting biases, the authors aimed to minimize their potential impact by ensuring a comprehensive search for eligible studies and by being alert for duplication of data. We did not use a funnel plot to explore the possibility of small study effects (i.e., a tendency for estimates of the intervention effect to be more beneficial in smaller studies), because such an analysis is useful only when at least ten studies are included.

Additional Analyses

We had planned to perform sensitivity analysis to verify whether the conclusions would have been different if eligibility was restricted to studies without high risk of bias.

Overall Quality of the Body of Evidence: Summary of Findings Table

A summary of findings table was generated with the use of Gradepro software. The quality of the evidence for the main review outcomes was evaluated using the following GRADE criteria: We considered the limitations of included studies (i.e., high risk of bias), inconsistency of effect, imprecision, indirectness, and publication bias. Judgments about evidence quality (high, moderate, low, or very low) were justified, documented, and incorporated into the reports of the results for each outcome (28).

RESULTS

Study Selection

The electronic search was performed on April 3, 2013, and a total of 264 records were retrieved: CENTRAL = 13; CINAHL = 2; Embase = 206; LILACS = 15; MEDLINE = 20; PsycINFO = 2; ClinicalTrials = 6; no additional records were obtained from Controlled-Trials, WHO, or OpenGrey or by hand searching the reference lists of

included studies and related reviews. We excluded 246 records after reading titles and abstracts: 42 were duplicates and 204 records clearly did not meet the eligibility criteria. We further examined 18 records for eligibility: Eight studies (from 11 records) were included (14, 20–26). Six studies (from seven records) were excluded for the following reasons: Two were not randomized (29, 30); one was a retrospective analysis (31); in one, cabergoline was used by all participants (32); one was ongoing, recruiting participants without preliminary results (33); and one was completed but not published study and the authors did not answer our e-mails (34). A flowchart describing the selection and inclusion of the studies is shown in Supplemental Figure 1.

Study Characteristics

Eight studies were included in this review, and their characteristics are reported in Table 1.

Design and settings. All included studies were parallel designed. Seven studies were single-center: One was conducted in Spain (14); three in Iran (22, 23, 26), one in Brazil (20), one in Israel (24), and one in Saudi Arabia (21). We were not able to identify the country where the other study was conducted, because its authors were from Egypt and the United Arab Emirates and the published abstract did not provide sufficient details about the setting (25). One study was blinded to patients, care providers, and outcome assessors (14), and the other seven studies were not blinded (open studies).

Source of information. The main reports used to extract data were abstracts published in conference proceedings in three studies (23–25) and full articles published in medical journals in five studies (14, 20–22, 26). We tried to contact authors from all of the studies, but additional details were provided for only one (26): The authors answered that their study was properly randomized.

Participants. A total of 858 women undergoing ART from seven studies were included in the pooled analyses: 408 allocated to cabergoline (alone or combined with another intervention) and 450 allocated to no treatment or other intervention. The eligibility criterion in all of the included studies was high risk for OHSS, but the definition of "high risk" varied across studies (Table 1): two studies considered it to be E_2 >4,000 pg/mL on the day of hCG injection (20, 24); two studies considered it to be ≥20 follicles >12 mm and >20 oocytes retrieved (14, 22); one study considered it to be E_2 >3,500 pg/mL on the day of hCG injection and 20 follicles >12 mm (21); another study considered it to be E_2 >3,000 pg/mL at hCG injection and ≥20 follicles ≤14 mm (26); one study considered it to be women with polycystic ovary syndrome undergoing COS with gonadotropins 200–300 UI/d (25); and one study did not specify the criteria used to define the group of women at high risk of OHSS (23).

Interventions. All included studies used different comparators with cabergoline, and the total doses and timing of interventions also varied across studies: 0.5 mg/d cabergoline for 8 days, compared with placebo for 8 days (14) or with no treatment (24), starting at hCG injection; 0.5 mg/d cabergoline for 3 weeks + 20 g albumin at oocyte retrieval, compared with 20 g albumin at oocyte retrieval (20); 0.25 mg/d cabergoline for 8 days, starting at hCG injection + 500 mL HES at oocyte retrieval, compared with 500 mL HES at oocyte retrieval (21); 0.5 mg/d cabergoline for 2 days, repeating after 1 week, starting at hCG injection, compared with two groups: no treatment and 20 mg/d prednisolone at hCG injection until pregnancy test (25); 0.5 mg/d cabergoline for 7 days, starting at oocyte retrieval, compared with 20 g albumin at oocyte retrieval (22); 0.5 mg/d cabergoline for 7 days, starting at hCG injection, compared with coasting (i.e., ceasing gonadotropin and withholding hCG injection until E_2 reaches <3,000 pg/mL) (26); and 0.5 mg/d cabergoline for 12 days, starting at oocyte retrieval, compared with 20 g albumin at oocyte retrieval (23).

Outcomes. No study reported congenital abnormalities; five studies reported clinical pregnancy, but only one of them reported live birth; seven studies reported OHSS, six of them distinguishing moderate and severe forms of OHSS, and one not making such distinction. The diagnostic criteria for OHSS were not the same in all of the included studies. Four studies (14, 21, 22, 26) used the criteria described by Golan et al. (35), one study (20) used the criteria described by Aboulghar and Mansour (9), and the two other studies (24, 25) were reported as conference abstracts and did not describe their criteria with sufficient detail. Although five studies reported clinical pregnancy, data from one of them (14) were not included in this review because cabergoline was used in oocyte donors and the pregnancies occurred in the recipients. Clinical pregnancy was defined by the presence of fetal heartbeat on ultrasound scan in three studies (20, 21, 26), and the other study did not specify the criterion used (22).

Five studies reported number of oocytes retrieved; three studies reported miscarriage. One study (23) was not included in the quantitative synthesis (meta-analysis) because we were not able to extract data for any of the evaluated outcomes (authors stated only that the OHSS occurrence was significantly reduced in the group using cabergoline).

Risk of Bias within Studies

The risk of bias summary of the included studies is reported in Supplemental Figure 2.

Random sequence generation. Five studies applied adequate methods (14, 20–22, 26), and three studies did not report which method was used (23–25).

Allocation concealment. Only one study reported having concealed the allocation sequence with the use of sealed envelopes (22).

Blinding of participants and personnel. Only one study reported blinding patients and care providers (14).

Blinding of outcome assessment. Only one study reported blinding of the personnel who performed transvaginal ultrasound to investigate the existence of ascites (14); all other studies did not report whether outcome assessors were blinded or not.

Incomplete outcome data. Two studies were judged to be at low risk of bias because the authors reported what happened

TABLE 1

Characteristics of included studies.

	Ahmadi 2010	Alvarez 2007	Amir 2011	Carizza 2008	Salah Edeen 2009	Shaltout 2012	Sohrabvand 2009	Tehraninejad 2012
Country	Iran	Spain	Israel	Brazil	United Arab Emirates or Egypt	Saudi Arabia	Iran	Iran
Funding sources	NR	NR	NR	NR	NR	None	NR	NR
Conflict of interests	None declared	None declared	NR	NR	NR	NR	None declared	NR
Ethical approval	NR	Yes	NR	Yes	NR	Yes	Yes	Yes
Signed informed consent	NR	Yes	NR	Yes	NR	Yes	Yes	Yes
Study design	Parallel design	Parallel design	Parallel design	Parallel design	Parallel design	Parallel design	Parallel design	Parallel design
Period of enrollment	NR	April 2004 to July 2006	NR	October 2005 to September 2007	NR	January 2007 to October 2010	April 2006 to March 2007	June 2009 to December 2010
Inclusion criteria	High risk for OHSS	Oocyte donors at high risk for OHSS (20–30 follicles >12 mm, and retrieval of >20 oocytes)	High risk for OHSS (E_2 >4,000 pg/mL on the day of hCG injection)	High risk for OHSS (E_2 >4,000 pg/mL on the day of hCG injection)	Women with PCOS undergoing ovarian stimulation with gonadotropins 200–300 UI/d rFSH in a long protocol	High risk for OHSS (E_2 >3,500 pg/mL on the day of hCG, and 20 follicles >12 mm)	High risk for OHSS (≥20 follicles in both ovaries, the majority being ≤ 14 mm in diameter, and E_2 >3,000 pg/mL on the day of hCG administration)	High risk for OHSS (20–30 follicles > 12 mm and retrieval of >20 oocytes)
Exclusion criteria	NR	Coasting	NR	NR	NR	Participants with E_2 >5,000 pg/mL	Participants in whom the use of dopamine agonists were contraindicated	Coasting, age >37 y, uterine surgery, submucosal and intramural fibromas >5 cm
Study groups	2	2	2	2	3	2	2	2
Comparison	Cabergoline vs. albumin	Cabergoline vs. placebo	Caberboline vs. no treatment	Cabergoline + albumin vs. albumin	Cabergoline vs. prednisolone or no treatment	Cabergoline + hydroxyethyl starch vs. hydroxyethyl starch	Cabergoline vs. coasting	Cabergoline vs. albumin
Interventions	0.5 mg/d cabergoline for 12 d starting on day of oocyte retrieval	0.5 mg/d cabergoline for 8 d starting on day of hCG injection	0.5 mg/d cabergoline for 8 d starting on day of hCG injection	0.5 mg/d cabergoline for 3 wk starting on the day after oocyte retrieval + 20 g albumin on day of oocyte retrieval	0.5 mg/d cabergoline for 2 d, repeating 1 wk later, starting from day of hCG injection	0.25 mg/d cabergoline for 8 d starting on day of hCG injection + 500 mL hydroxyethyl starch on the day of oocyte retrieval	0.5 mg/d cabergoline for 7 d starting on day of hCG injection	0.5 mg/d cabergoline for 7 d starting on day of oocyte retrieval
Comparator	20 g albumin on day of oocyte retrieval	Placebo for 8 days	No treatment	20 g albumin on day of oocyte retrieval	Two groups: 1) 10 mg prednisolone twice per day starting on day of hCG until date of pregnancy test; 2) no treatment	500 mL hydroxyethyl starch on day of oocyte retrieval	Coasting (gonadotropin was ceased until E_2 reached <3,000 pg/mL before hCG administration)	20 g albumin on day of oocyte retrieval

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TABLE 1

Continued.

	Ahmadi 2010	Alvarez 2007	Amir 2011	Carizza 2008	Salah Edeen 2009	Shaltout 2012	Sohrabvand 2009	Tehraninejad 2012
Pituitary suppression	Unclear	GnRH agonist (long protocol)	Unclear	GnRH agonist (long protocol), 0.5–1.0 mg/d leuprolide acetate	Unclear	GnRH agonist (long protocol), 0.1 mg/d triptorelin	GnRH agonist (long protocol), 0.5 mg/d buserelin	GnRH agonist (long protocol), 0.5 mg/d buserelin
Follicle stimulation	Unclear	rFSH or hMG	Unclear	rFSH	rFSH	hMG	rFSH	rFSH
Triggering	Unclear	hCG (dose NR)	Unclear	Recombinant hCG (0.25 mg)	Unclear	hCG (5,000 IU)	hCG (10,000 IU)	hCG (10,000 IU)
Moderate OHSS/ severe OHSS criteria	NR/NR	Ascites on TVUS/ clinically evident ascites or hydrothorax or one of the following: hemoconcentration, coagulopathy, liver or renal dysfunction	Ascites on TVUS/ hemoconcentration, liver and renal dysfunction	Ascites on TVUS or clinical signs (pain, nausea, distension)/ clinically evident ascites or hydrothorax, dyspnea, oliguria, hemoconcentration, renal or liver dysfunction	Ascites on TVUS/NR	Ascites on TVUS/ clinically evident ascites or hydrothorax, dyspnea, hemoconcentration, coagulopathy, liver or renal dysfunction	Ascites on TVUS/ clinically evident ascites or hydrothorax, dyspnea, hemoconcentration, coagulopathy, liver or renal dysfunction	Ascites on TVUS/ clinically evident ascites or hydrothorax, dyspnea, hemoconcentration, coagulopathy, liver or renal dysfunction
Clinical pregnancy definition	NR	NR	NR	Presence of fetal heart beat on ultrasound scan; did not specify timing of the diagnosis	NR	Presence of fetal heart pulsation 2 wk after a positive β-hCG test	β-hCG level was checked 2 wk after embryo transfer and clinical pregnancy was confirmed 2 wk later by sonographic detection of the gestational sac	Reported "chemical pregnancy" and "clinical pregnancy" as separate outcomes, but did not specify these outcomes' definitions
Age (y)	NR	24.6 ± 0.7 vs. 24.0 ± 0.8; NS	NR	34.0 ± 4.6 vs. 33.6 ± 4.7; NS	NR	27.6 ± 3.6 vs. 27.9 ± 3.8; NS	29.9 ± 3.6 vs. 29.2 ± 3.5; NS	29.03 ± 3.2 vs. 28.08 ± 8.6; NS
BMI (kg/m^2)	NR	22.1 ± 0.4 vs. 22.2 ± 0.5; NS	NR	21.1 ± 2.6 vs. 21.3 ± 2.9; NS	NR	24.6 ± 2.7 vs. 25.0 ± 3.3; NS	26.4 ± 3.8 vs. 27.8 ± 3.2; NS	24.8 ± 3.3 vs. 24.9 ± 3.8; NS
Proportion of IVF/ICSI	NR	NR	NR	Only ICSI	NR	NR	NR	NR
Implantation rate (n/N and/or %)	NR	Only included oocyte donors	NR	60/271 (22.1%) vs. 49/258 (19.0%); NS	NR	NR	NR	Presented rates (53% and 54%) are incompatible with the other results
Study objectives	To compare cabergoline and albumin effectiveness in reducing OHSS in high-risk women	To examine whether cabergoline reduces OHSS in high-risk women	To examine whether cabergoline reduces OHSS in high-risk women	To examine whether cabergoline reduces OHSS in high-risk women	To examine whether cabergoline and/or prednisolone reduces OHSS in high-risk women	To examine whether low-dose cabergoline reduces OHSS in high-risk women	To compare cabergoline and coasting in decreasing the occurrence of OHSS in high-risk women	To compare cabergoline and albumin effectiveness in reducing OHSS in high-risk women

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TABLE 1

Continued.

	Ahmadi 2010	Alvarez 2007	Amir 2011	Carizza 2008	Salah Edeen 2009	Shaltout 2012	Sohrabvand 2009	Tehraninejad 2012
Authors' conclusions	Cabergoline is more effective than intravenous human albumin for the prevention of OHSS.	Dopamine agonists can be used for the prevention of OHSS in women undergoing ART.	Cabergoline can be used for the management of high-risk patients undergoing ART.	Cabergoline administration was associated with the absence of "early"-onset OHSS, dearly attributable to the use of the drug.	Cabergoline has a significant role in prevention of OHSS in PCOS women.	Cabergoline, reduces OHSS incidence in high-risk patients without jeopardizing the pregnancy outcomes.	Cabergoline seems to be an effective, convenient, and safe drug for the prevention of OHSS.	Cabergoline is better than human albumin for decreasing the incidence and severity of OHSS.

Note: Data presented as Cabergoline group versus control group. ART = assisted reproductive technologies; BMI = body mass index; ICSI = intracytoplasmic sperm injection; NR = not reported; OHSS = ovarian hyperstimulation syndrome; PCOS = polycystic ovary syndrome; TVUS = transvaginal ultrasound.

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to all randomized patients and an analysis respecting the ITT principle could be performed (21, 26). Four studies were judged to be at unclear risk of bias. In three of those studies, attrition rates were <5% and were equally distributed among the groups, but it was not possible to confidently assume that attrition could not have biased the results (20, 22, 25), and in the other study there was insufficient information to provide judgment (23). The other two studies were judged to be at high risk of bias because of significant attrition rates (14, 24).

Selective reporting. We could locate the protocol for two studies (14, 22), and all proposed outcomes were reported. Although we could not locate a protocol for the other six studies, all outcomes described in the methods section were appropriately reported and we did not suspect reporting bias. Therefore, all of the studies were considered to be at low risk of bias.

Other bias. We did not suspect other sources of bias for any of the included studies.

Results of Individual Studies

The results of the individual studies are reported in the forest plots (Figs. 1 and 2; and Supplemental Figs. 3–7).

Synthesis of Results

OHSS. Moderate or severe pooled analysis demonstrated benefit with cabergoline administration during COS: RR 0.38, 95% CI 0.29–0.51, $P<.00001$, 7 studies, 858 women; $I^2 = 0\%$; moderate-quality evidence (Fig. 1). The estimated NNTB was six women (95% CI 5–7).

Moderate pooled analysis demonstrated benefit with cabergoline administration during COS: RR 0.41, 95% CI 0.29–0.58, $P<.00001$, 6 studies, 665 women; $I^2 = 0\%$; moderate-quality evidence (Supplemental Fig. 3). The estimated NNTB was 6 women (95% CI 5–8).

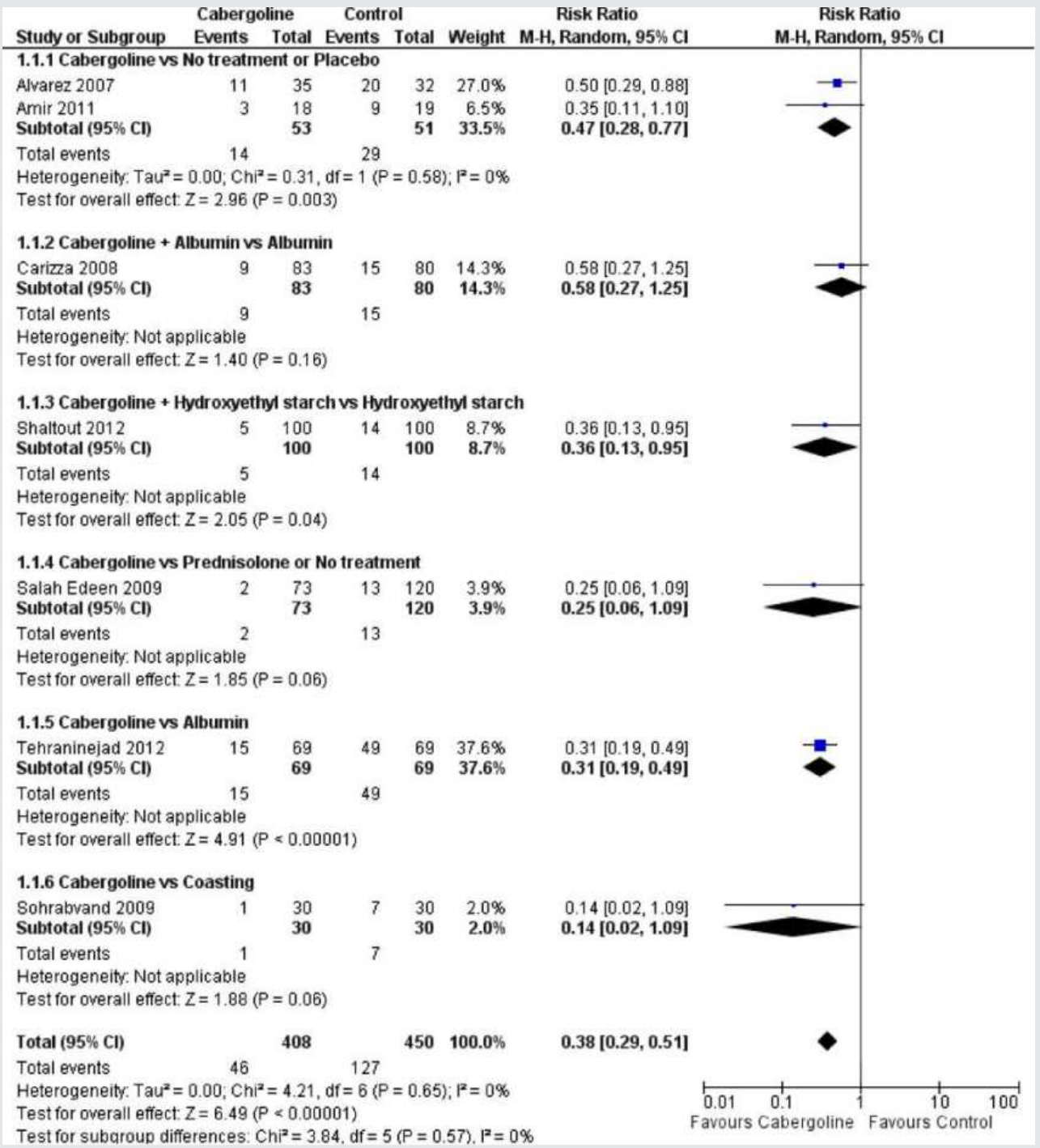
Severe pooled analysis demonstrated benefit with cabergoline administration during COS: Peto OR 0.30, 95% CI 0.15–0.60, $P=.0008$, 6 studies, 665 women; $I^2 = 48\%$; moderate-quality evidence (Supplemental Fig. 4). The estimated NNTB was 18 women (95% CI 14–31).

Live birth. Only one study reported the number of live births. The CI was wide and we did not have sufficient precision to identify whether cabergoline causes substantial harm, no effect, or substantial benefit: RR 1.03, 95% CI 0.71–1.48, $P=.88$, 1 study, 200 women, low-quality evidence (Supplemental Fig. 5).

Clinical pregnancy. Although the CI was also relatively wide, it suggests that cabergoline is unlikely to have a substantial impact in clinical pregnancy: RR 1.02, 95% CI 0.78–1.34, $P=.86$, 4 studies, 561 women, low-quality evidence (Fig. 2).

Number of oocytes retrieved. The CI was wide and we did not have sufficient precision to identify whether cabergoline causes no effect or benefit: MD 1.15, 95% CI −0.76 to 3.07, $P=.24$, 5 studies, 628 women; $I^2 = 65\%$; low-quality evidence (Supplemental Fig. 6). The observed heterogeneity can be easily explained by the different comparisons used

FIGURE 1



Forest plot for moderate or severe ovarian hyperstimulation syndrome per allocated woman. CI = confidence interval; M-H = Mantel-Haenszel.

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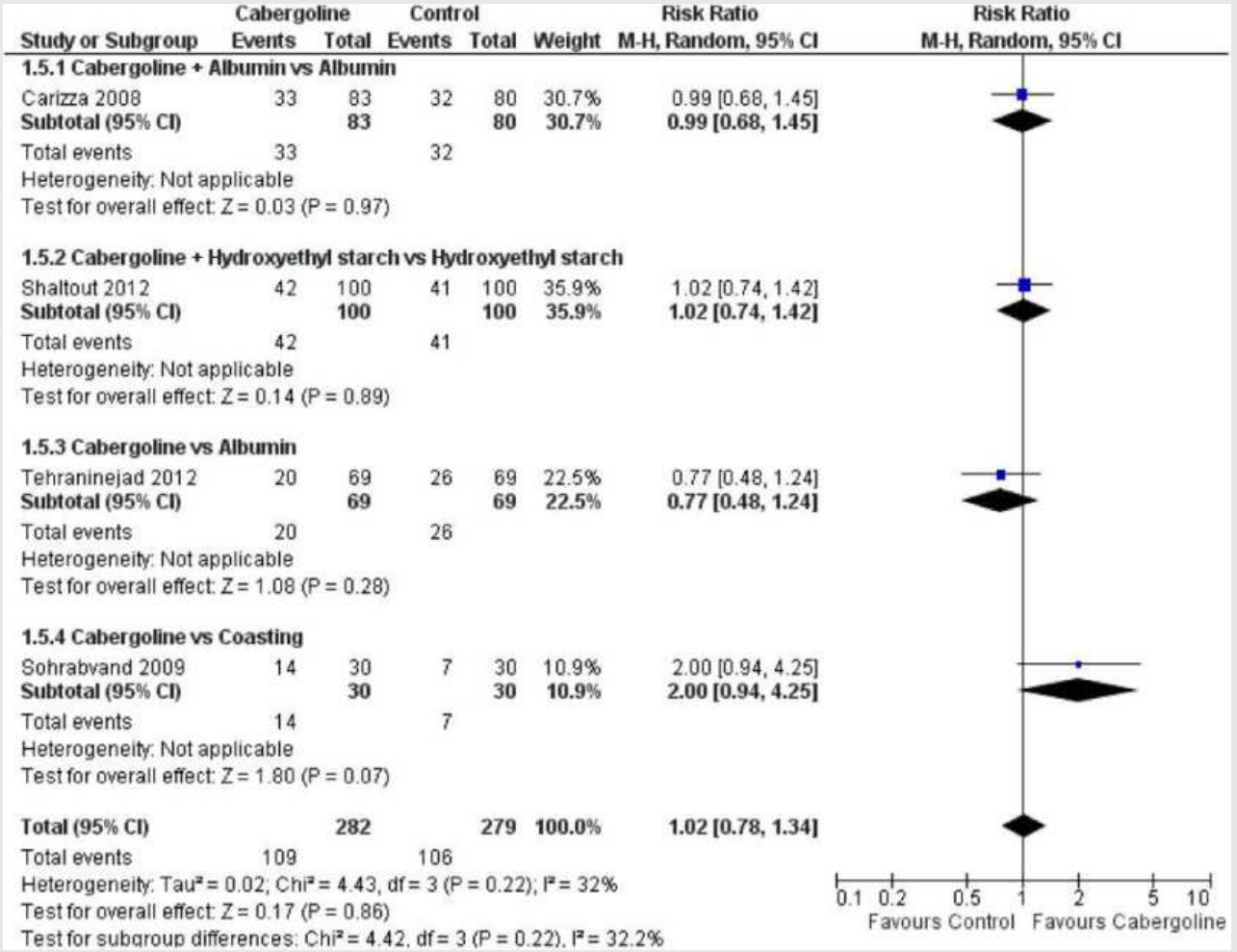
across the studies; whereas cabergoline seems to improve the number of oocytes retrieved compared with coasting (21), a similar number of retrieved oocytes was observed in the other comparisons.

Miscarriage. The CI was very wide and we did not have sufficient precision to identify whether cabergoline causes substantial harm, no effect, or substantial benefit: RR 0.69, 95% CI 0.27–1.76, P=.44, 3 studies, 194 women; I^2 = 0%; very-low-quality evidence (Supplemental Fig. 7).

Risk of bias across studies. We did not identify any evidence of publication bias. However, the analysis is suboptimal because we did not perform a funnel plot analysis. Such analysis would have been performed only if ten or more studies were included in the review.

FIGURE 2



Forest plot for clinical pregnancy per allocated woman. Abreviations as in Figure 1.

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Additional analyses. We did not perform any sensitivity analysis, because all included studies were considered to be at high risk of bias. Although we included studies that compared cabergoline with various other interventions, and reported the results for each comparison separately, we still chose to pool the studies' results in a meta-analysis for each outcome, because the only perceived difference between the experimental and control groups was the use of cabergoline. However, because the different comparators could result in heterogeneity among the studies, we preferred to perform random-effects meta-analyses, which incorporate the assumption that the interventions were not the same across all studies, and result in more conservative estimates (27).

DISCUSSION

Summary of the evidence (Table 2)

Eight studies were included in the comparison of cabergoline vs. no cabergoline, two of them comparing cabergoline with placebo or no treatment, one comparing cabergoline + albumin with albumin, one comparing cabergoline + HES with HES, two comparing cabergoline with albumin, one comparing cabergoline with coasting, and one comparing cabergoline with prednisolone or no treatment. Seven of the eight studies were included in the pooled analyses. All of those seven studies reported OHSS, and pooled analyses demonstrated that cabergoline administration causes benefit, reducing the number of OHSS events (moderate, severe, and moderate + severe events). Only one study reported live births, and the effect estimate was not precise enough to define whether cabergoline causes harm, no effect, or benefit. Clinical pregnancy was reported in four studies and miscarriage in three studies. For these two outcomes, the estimated effect was not sufficiently precise to ascertain whether cabergoline causes harm, no effect, or benefit. The number of oocytes retrieved was reported in five studies; the estimated effect was not sufficiently precise to ascertain whether cabergoline causes no effect or benefit. No study reported congenital abnormalities.

TABLE 2

Summary of findings table: comparison of "cabergoline" versus "no cabergoline" for women at high risk of ovarian hyperstimulation syndrome (OHSS).

	Assumed risk without cabergoline	Corresponding risk with cabergoline (95% CI)	Relative effect (95% CI)	NNT (95% CI)	No. of participants (studies)	Quality of the evidence
OHSS (moderate or severe)	28.2%	10.7% (8.2%–14.4%)	RR 0.38 (0.29–0.51)	6 (5–7)	858 (7)	Moderate[a]
Severe OHSS	7.9%	2.5% (1.3%–4.9%)	OR 0.30 (0.15–0.60)	18 (14–31)	628 (5)	Moderate[a]
Moderate OHSS	26.7%	10.9% (7.7%–15.5%)	RR 0.41 (0.29–0.58)	6 (5–8)	665 (6)	Moderate[a]
Live birth	36.0%	37.1% (25.6%–53.3%)	RR 1.03 (0.71–1.48)	–	200 (1)	Low[b]
Clinical pregnancy	38.0%	38.8% (29.6%–50.9%)	RR 1.02 (0.78 to 1.34)	–	674 (5)	Low[b]
Miscarriage per clinical pregnancy	11.1%	7.7% (3.0%–19.5%)	RR 0.69 (0.27–1.76)	–	194 (3)	Very low[c]
Oocytes retrieved	22.6 oocytes	23.8 oocytes (21.0–25.7)	MD 1.15 (−0.8 to 3.1)	–	628 (5)	Low[b]
Congenital abnormalities			No study reported this outcome			

Note: The basis for the assumed risk is the median risk in the groups without cabergoline across studies. The corresponding risk (and its 95% CI) is based on the assumed risk and the relative effect of the intervention (and its 95% CI). GRADE Working Group grades of evidence: high quality: further research is very unlikely to change our confidence in the estimate of effect; moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very low quality: we are very uncertain about the estimate. CI = confidence interval; MD = mean difference; NNT = number needed to treat; OR = odds ratio; RR = risk ratio.

[a] Downgraded one level for quality of the included studies.

[b] Downgraded one level for imprecision and one level for quality of the included studies.

[c] Downgraded two levels for serious imprecision and one additional level for quality of the included studies.

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Study Limitations

All included studies were judged to be at high risk of bias, reducing the overall quality of the evidence. We could extract data for quantitative analyses in only seven of the eight included studies. Only one of the included studies reported live birth rates, and the estimates were imprecise for ascertaining the effect of the intervention. Although we pooled the studies' results with the use of random-effects meta-analyses, which account for possible differences among the effects of the interventions and generate more conservative pooled estimates, the heterogeneity found in the comparator interventions across the studies should be considered when interpreting the results for each outcome. The assessment of publication and reporting bias was suboptimal, owing to the impossibility of performing a funnel plot analysis.

Quality of the Evidence

For OHSS (moderate, severe, and moderate + severe), the evidence was considered to be of moderate quality, downgraded one level for quality of the included studies. The evidence was considered to be of low quality for live birth, being downgraded one level for imprecision (wide 95% CI) and one additional level for quality of the only included study. Evidence for clinical pregnancy and for number of retrieved oocytes was considered to be of low quality, downgraded one level for imprecision and another level for quality of the included studies. For miscarriage, evidence was judged to be of very low quality, downgraded two levels for serious imprecision and one additional level for quality of the included studies.

Overall Completeness and Applicability of the Evidence

Pooled analyses of the included RCTs allowed us to ascertain that cabergoline reduces the occurrence of moderate-severe forms of OHSS in women at high risk undergoing COS. The estimates for severe forms of OHSS only, albeit precise for benefit of the intervention, must be interpreted with caution owing to the rarity of these events and the consequent difficulty in drawing precise estimates. Additionally, differences between moderate and severe forms might not always be so clear. For live births and miscarriage, pooled estimates were not precise enough, and we are still uncertain of the effect of cabergoline over such outcomes. Conversely, although the effect estimates of cabergoline on clinical pregnancy were also relatively imprecise (RR 1.02, 95% CI 0.78–1.34), the intervention is unlikely to cause any clinically significant impact. Regarding the number of oocytes, some heterogeneity was observed across the studies, which can be easily explained by the different comparators. However, it seems unlikely that cabergoline causes a clinically relevant reduction in the number of the oocytes retrieved.

In addition to the seven studies included in the quantitative synthesis, the other included study reported that the risk of OHSS is reduced when using cabergoline (23), which is in accordance with the results of our meta-analysis. One study excluded for not being a randomized trial (29) also addressed

the review question, comparing cabergoline (alone or combined with albumin) vs. albumin alone: In agreement with the findings of our review, those authors observed a reduction in the occurrence of the moderate-severe forms of OHSS; however, estimates were imprecise (RR 0.33, 95% CI 0.07 with 1.65). Additionally, several other published reviews agree that cabergoline is an effective intervention to reduce the risk of OHSS (8, 18, 36–40).

CONCLUSION

Cabergoline reduces the incidence of OHSS when used by women who are at high risk for that complication while undergoing COS. Although the estimates were imprecise, cabergoline probably does not have a clinically relevant impact on clinical pregnancy rates or on the number of retrieved oocytes. However, we are still uncertain of the effects of cabergoline on important outcomes, namely, live birth, miscarriage, and congenital abnormalities. Future research examining these outcomes should be encouraged.

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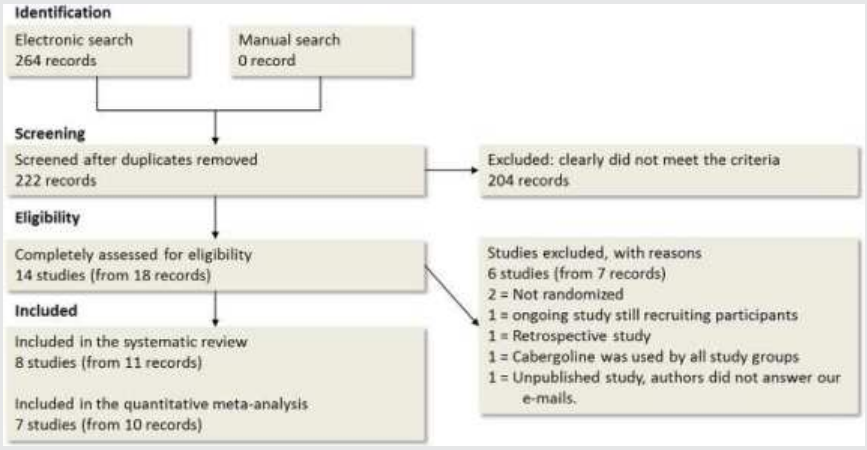
SUPPLEMENTAL FIGURE 1



Flowchart of study selection.

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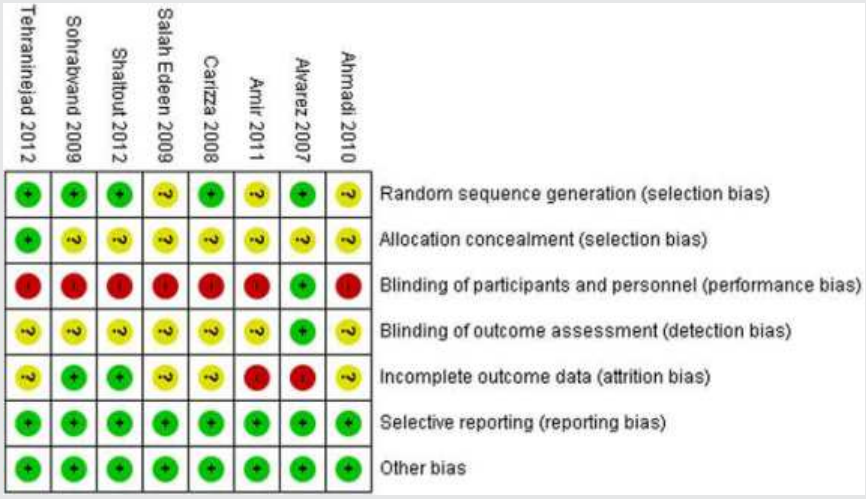
SUPPLEMENTAL FIGURE 2



Risk of bias summary for the included studies.

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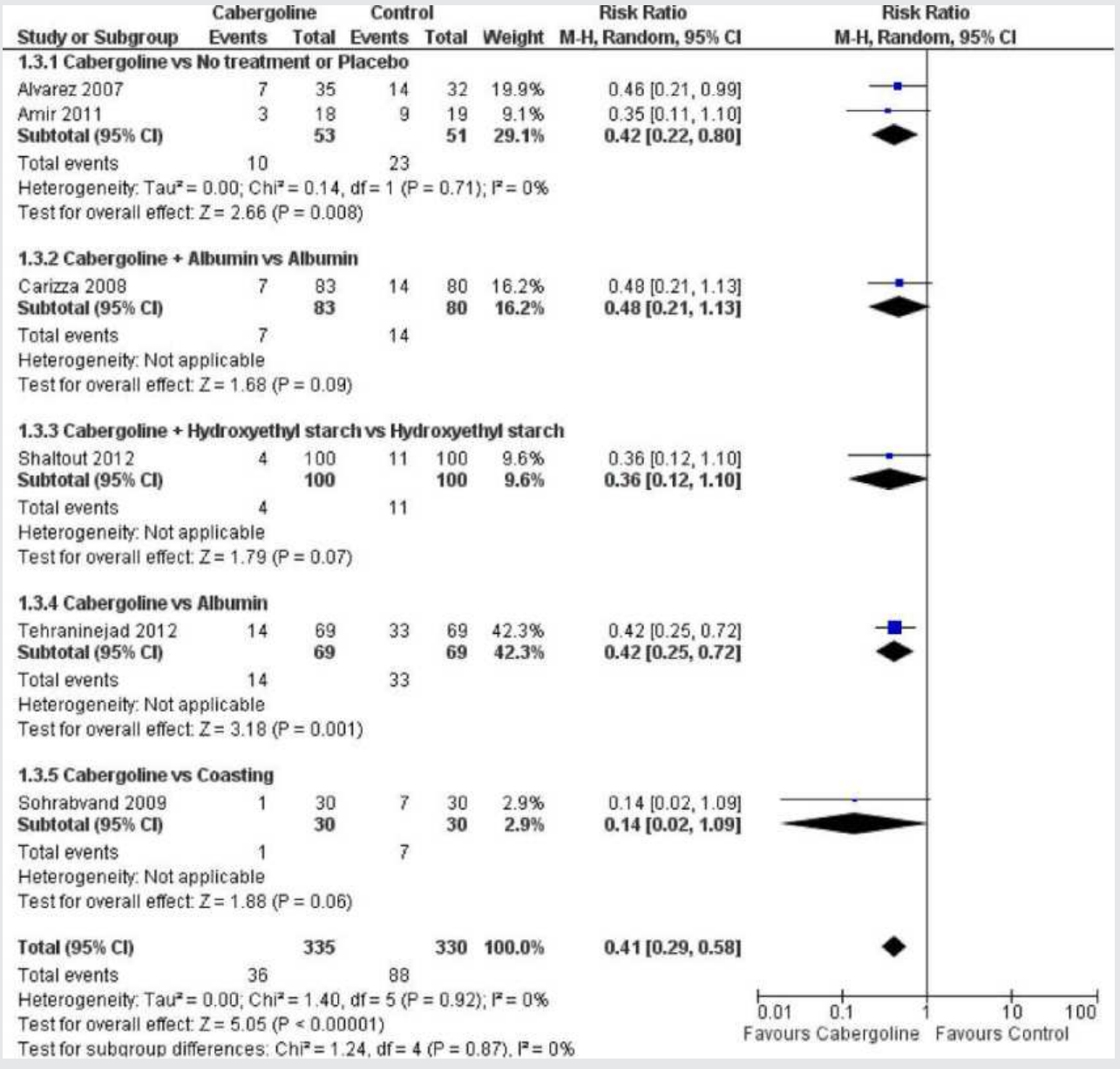
SUPPLEMENTAL FIGURE 3



Forest plot for moderate ovarian hyperstimulation syndrome per allocated woman. CI = confidence interval; M-H = Mantel-Haenszel.

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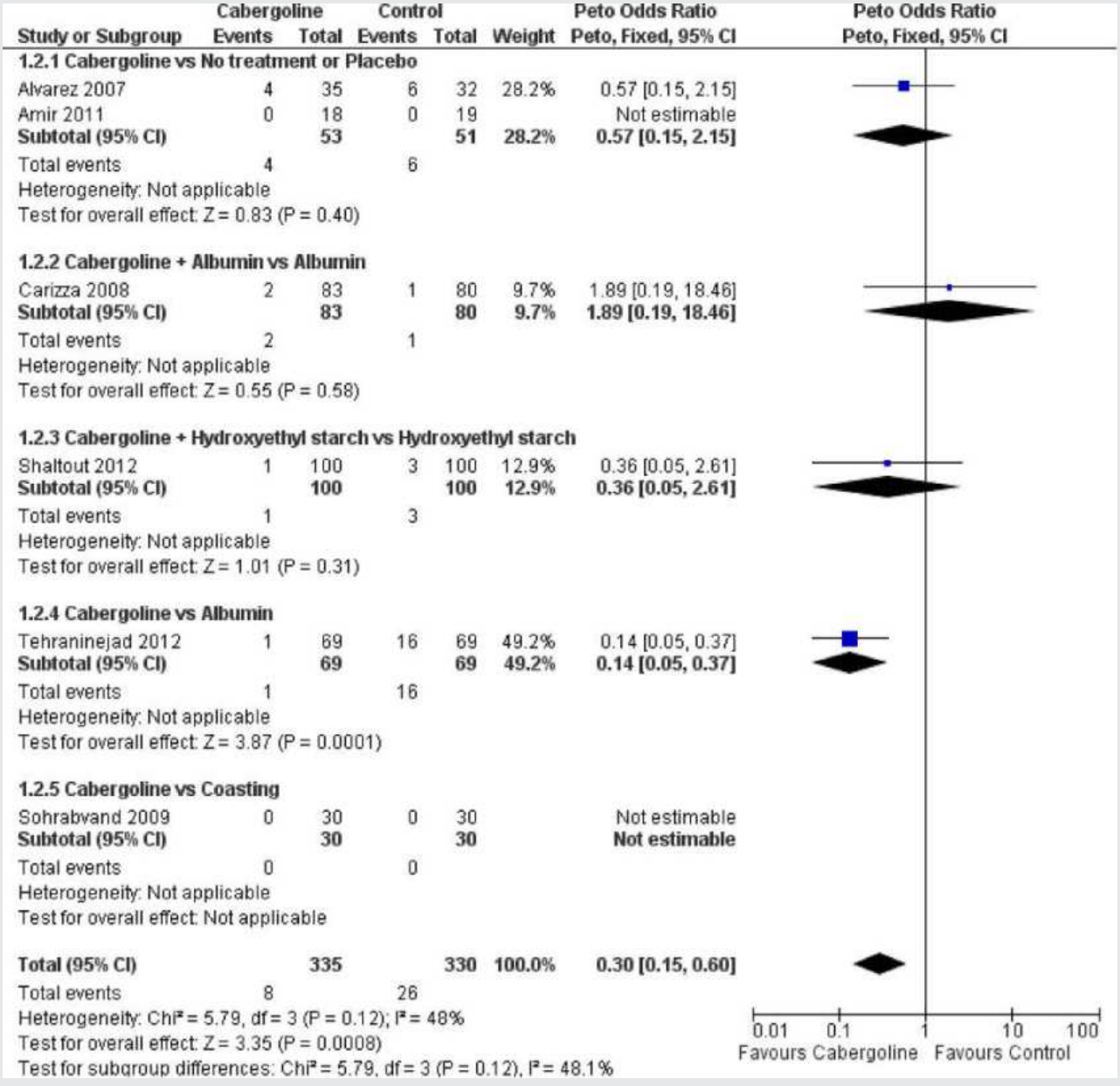
SUPPLEMENTAL FIGURE 4



Forest plot for severe ovarian hyperstimulation syndrome per allocated woman. CI = confidence interval.

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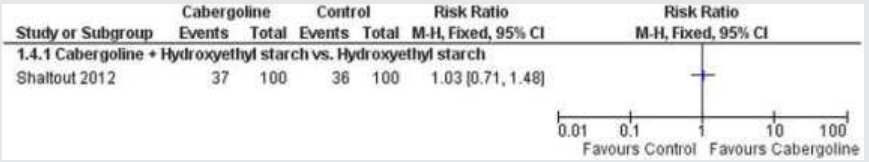
SUPPLEMENTAL FIGURE 5



Forest plot for live birth per allocated woman. Abbreviations as in Supplemental Figure 3.

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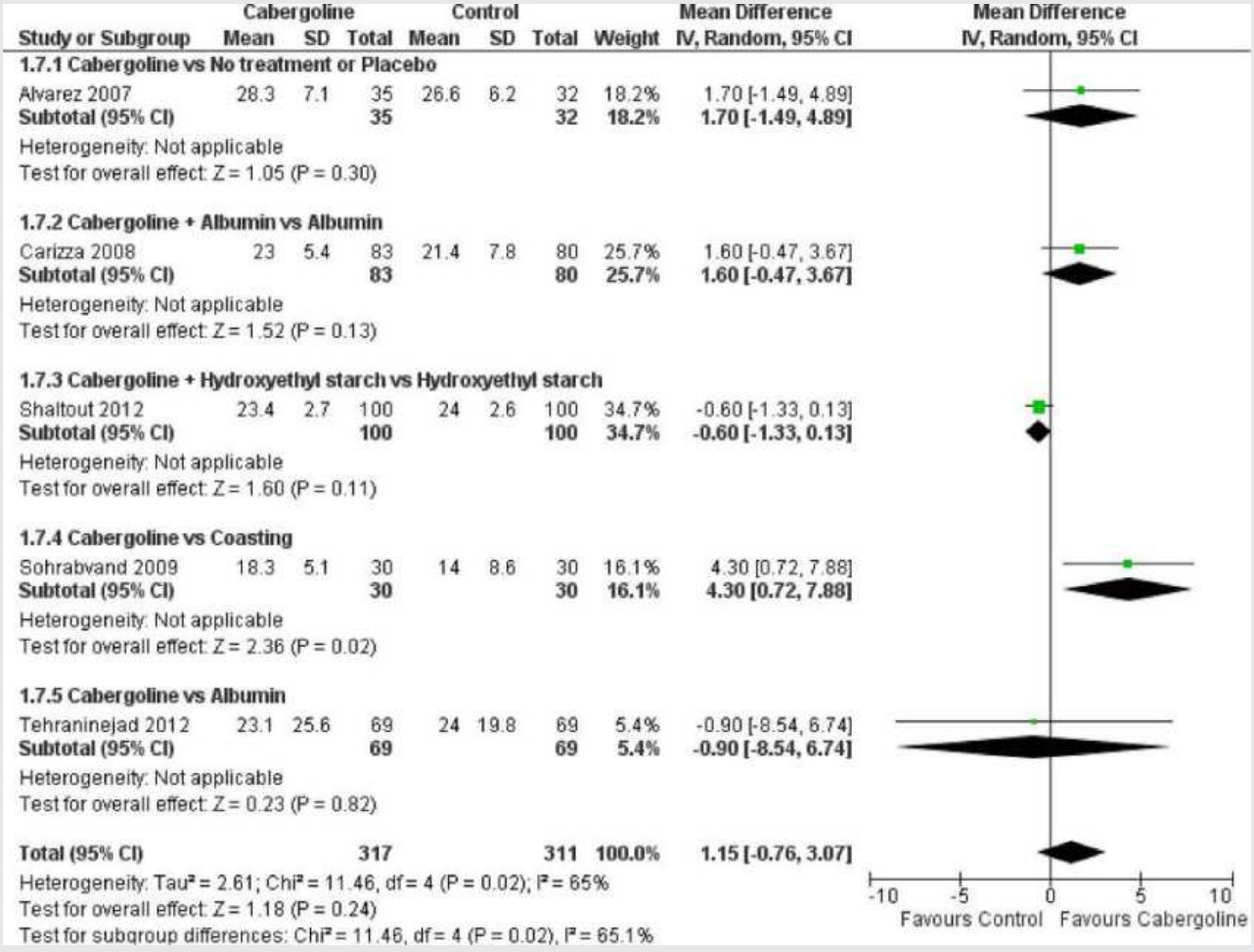
SUPPLEMENTAL FIGURE 6



Forest plot for number of oocytes retrieved per allocated woman. CI = confidence interval; IV = inverse variance.

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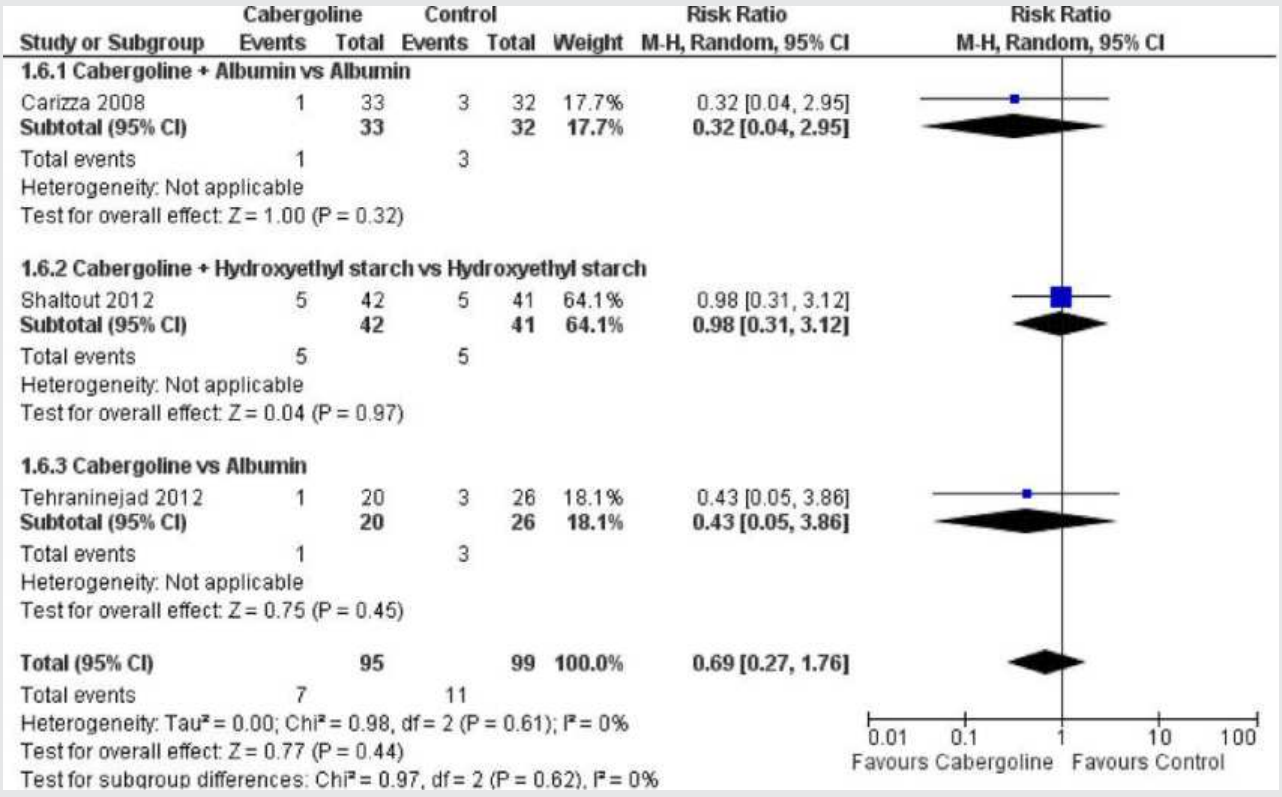
SUPPLEMENTAL FIGURE 7



Forest plot for miscarriage per clinical pregnancy. Abbreviations as in Supplemental Figure 3.

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