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The Influence of Cabergoline and Coasting in Prevention of the Ovarian Hyperstimulation Syndrome in Patients Undergoing IVF/ICSI-ET Treatment: A Systematic Review and Meta-Analysis

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Abstract

Objective: To compare the effectiveness of two methods in preventing ovarian hyperstimulation syndrome (OHSS) with cabergoline and coasting. **Design:** Systematic review and meta-analysis of randomized clinical trials (RCTs). **Patients:** Women were considered as have risk of OHSS undergoing fertility treatment. **Interventions:** Cabergoline, coasting. **Result:** There were included five RCT studies. The clinical pregnancy rate was no significantly difference between two groups (RR 1.22, 95% CI [0.86, 1.71]), implantation rate (RR 1.00, 95% CI [0.75, 1.32]), severe OHSS (RR 0.93, 95% CI [0.38, 2.31]), fertilization rate (SMD 0.70, 95% CI [−0.10, 1.50]), number of oocytes retrieved (SMD 0.80, 95% CI [0.30, 1.30]), number of embryo transfer (SMD-0.04, 95% CI [−0.24, 0.17]), E_2 value on the day of HCG injection (SMD 0.21, 95% CI [−0.25, 0.68]), number of MII oocytes (SMD 0.71, 95% CI [0.32, 1.11]), abortion rate (RR 0.61, 95% CI [0.21, 1.83]), number of follicles > 17 mm on day of HCG (SMD -0.01, 95% CI [−0.26, 0.24]), number of follicles 15 - 17 mm on day of HCG (SMD −0.08, 95% CI [−0.33, 0.17]), number of follicles 10 - 14 mm on day of HCG (SMD −0.06, 95% CI [−0.31, 0.19]). **Conclusion:** Both cabergoline and coasting prevent the occurrence of OHSS, but no statistically significant difference between them. Compared with coasting group, a daily dose of 0.5 mg cabergoline significantly increased the number of oocytes retrieved, MII oocytes, and fertilization rate, but decreased the abortion rate.

Keywords

Cabergoline, Coasting, Ovarian Hyperstimulation Syndrome (OHSS), Ovulation Induction

1. Introduction

In the light of the latest figures, the number of infertility predicted is up to 186 million [1]. With the popularization and widespread application of modern assisted reproductive technology, the incidence of ovarian hyperstimulation syndrome (OHSS) as an iatrogenic injury affected 1% - 14% of *in vitro* fertilization cycles [2]. It usually has a self-limited course with unfavorable outcome when under the treatment of controlled ovarian stimulation, therefore received widespread attention by reproduction specialist in reproductive centers all around the world.

At present the pathological mechanism of the OHSS is not yet clear, consequently the treatment of OHSS is symptomatic treatment or expectant management, and prevention and timely detection is the key to treatment. Nowadays, the treatment of OHSS is mainly depended on each individual fertility doctors' experience. There is no substantive or strict guideline for doctors. Cabergoline [3], coasting [4], albumin [5], calcium supplements [6], aspirin [7] are the commonly used interventions. The most popular therapeutic method on prevention of OHSS is coasting [8], and cabergoline is a relatively definitive drug for preventing OHSS in recent years.

The results of recent years have shown that cabergoline is more effective than placebo group to prevent the occurrence of OHSS [9] [10] [11] [12]. However, it was greater in the cabergoline group than in the hydroxyethyl starch (HES) group. Until now, there is no meta-analysis comparing the effects of cabergoline and coasting in the prevention of the occurrence of OHSS.

Our study is to compare the risk and effectiveness of using cabergoline or coasting in women who under the treatment of IVF/ICSI-ET in order to provide better guidance for clinical work.

2. Materials and Methods

2.1. Retrieval Strategies

Methods:

This study did not directly treat patient, therefore ethical committee approval is not necessary. We searched in Pubmed, Medicine, Cochrane library, Embase, and Springer-Link with the terms of (Ovarian Hyperstimulation Syndrome) or (OHSS) and (cabergoline) and (coasting) and (dopamine agonists) and (IVF) in title and abstract as of March 2020. No restrictions on language were imposed when searching for documents. Meanwhile, we extracted the corresponding data from the articles, including rate of clinical pregnancy, the occurrence of OHSS,

number of retrieved oocytes, number of MII oocytes, implantation rate. The comparison was shown by the risk ratios (RRs) or Std Mean Differences (SMD) with their 95% confidence intervals (CIs). We also searched and screened the corresponding references at the end of the selected articles.

2.2. Inclusive Criteria

The inclusion criteria are as follows: 1) The population of study was high-risk OHSS patients who undergoing IVF or Intracytoplasmic Sperm Injection (ICSI) and received the GnRha long protocol; 2) The included articles were randomized controlled trials (Randomized Controlled Trials, RCT), the treatment including cabergoline and coasting; 3) The results included the rate of clinical pregnancy, implantation rate, severe OHSS, number of MII oocytes, abortion rate.

2.3. Literature Screening and Data Extraction

The abstracts of all keywords retrieved by the two researchers were jointly screened. (Lin Liu and Xin Wang). Cross-checked and qualified abstract were evaluated separately by two researchers (Jie Jyu and Tonghui Meng). The divergent on abstract of the two researchers were resolved through discussion or submitting to a third party for assistance. If the abstract of the article meets the criteria, then two researchers (Fang Lyu and Xiaomei Zhang) carefully read and evaluate the full text. The extracted content mainly includes: 1) basic information, including the first author, the time of publication, 2) the basic situation of the research object, 3) the specific details of the intervention, 4) the key elements of the risk assessment, 5) the end of concern indicator and result measurement data.

2.4. Statistical Analysis

We used Review Manager 5.3 for statistical analysis. Data are showed by mean ± standard deviation or percentage (%). The results are expressed by the risk ratios (RRs) or Std. Mean Differences (SMD) and their 95% confidence intervals (CIs). The heterogeneity between the included studies was analyzed by the χ^2 test, and I^2 and P value were used to assess the heterogeneity between the articles. If the $I^2 = 0$ or $P > 0.10$, there is no statistical heterogeneity among the results of these studies, the Mantel-Haenszel fixed-effects model is used for meta-analysis. Otherwise, random-effects model was used for analysis after eliminated the effect of obvious clinical heterogeneity, and further analysis of heterogeneity sources is necessary. Significant clinical heterogeneity is treated by subgroup analysis or sensitivity analysis or only descriptive analysis. Since the number of included studies is less than 10, the funnel plot was not applicable.

2.5. Evaluation the Risk of Bias

The risk of bias summary is done by the two researchers in subject to the Cochrane handbook for systematic reviews of interventions version 5.1.0 [13]. The review authors judged the risk of biased item for every article included in the study.

3. Results

3.1 Literature Retrieval Results

A total of 425 articles were initially identified. After by layer screening, only 5 [14] [15] [16] [17] [18] studies met criteria, including 421 women. Document screening process and results shown in **Figure 1**.

3.2. Basic Characteristics of the Studies and Bias Risk Assessment

The basic characteristics of the study were shown in **Table 1**. The results of bias risk assessment were shown in **Figure 2** and which were judged by two independent reviewers. When encountering non-conformity, they jointly seek solutions from the third reviewer, and discussion again to solve the solution.

3.3. Meta-Analysis Results

3.3.1. Pregnancy Rate

Of the 5 articles included, only 4 [14] [15] [16] [18] reported rate of clinical pregnancy (**Figure 3(a)**). There were no statistical significance difference between the two groups (RR 1.22, 95% CI 0.86 - 1.71; $P > 0.05$), $I^2 = 23\%$, suggested that there was a low degree of heterogeneity between the studies. And subgroup analysis based on different countries was performed. When the participants were all from Iranian, the comparison of pregnancy rate between the two groups was statistically different. $I^2 = 0$, suggested that there was no heterogeneity between the articles, the results demonstrated that the pregnant rate of the cabergoline group was better than coasting group (RR 2.00, 95% CI 1.08 - 3.72; $P < 0.05$). But in the other subgroup, there was no statistical significance (RR 1.04, 95% CI 0.79 - 1.36; $P = 0.78$).

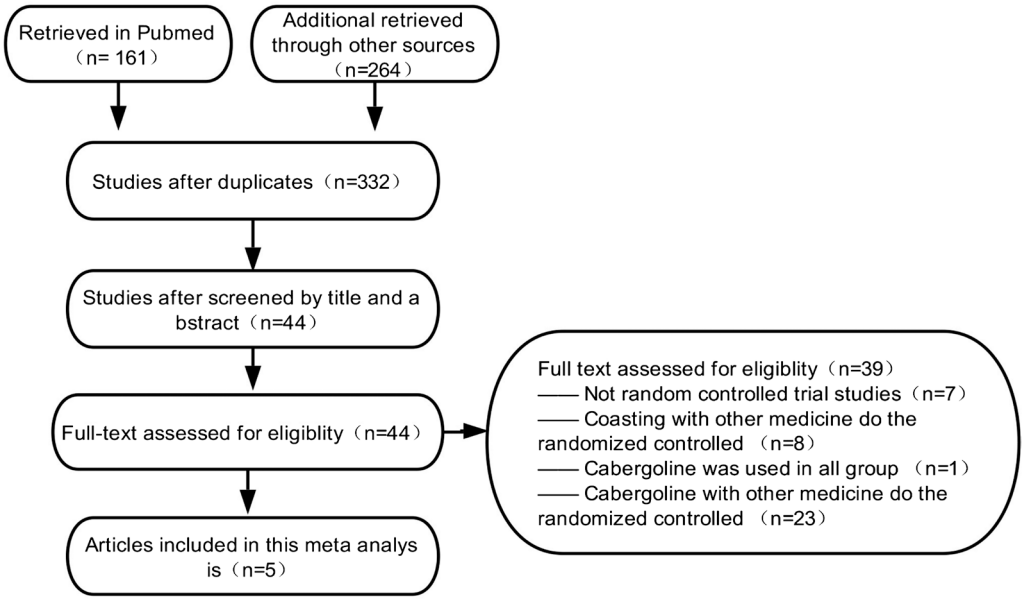


Figure 1. Flowchat of study selection. Overall, 425 studies were retrieved from databases of Pubmed, Medicine, Cochrane library, Embase, and Springer-Link. After removal of the duplicated and unrelated studies, five studies were included in this research.

Table 1. Characteristics of included studies.

	Aflatoonian *et al.* [15] 2008	**Sohrabvand *et al.* [16] 2009**	**Abdelaal *et al.* [17] 2012**	**Esinler *et al.* [14] 2013**	**Bassiouny *et al.* [18] 2018**
Country	Iran	Iran	Egypt	Turkey	Egypt
Number of patients	30 vs. 30	30 vs. 30	28 vs. 16	17 vs. 40	100 vs. 100
Conflict of Interests	No stated	None declared	None declared	None declared	None declared
Signed informed consent	Yes	Yes	Yes	No stated	Yes
Period of enrollment	7, 2006 and 7, 2007	4, 2006 to 3, 2007	3, 2010 and 8, 2011	2001-2011	10, 28, 2013, and 7, 31, 2015
Study groups	2	2	3	2	3
Study design	Parallel design	Parallel design	Parallel design	Parallel design	Parallel design
Ethical Approval	Yes	Yes	Yes	Yes	Yes
Method of allocation	No stated	No stated	No stated	Through computerized IVF database system	sealed opaque envelopes
Proportion of IVF/ICSI	IVF or ICSI cycles	No stated	Only ICSI	Only IVF	IVF or ICSI cycles
Age(y)	29.63±4.42 vs. 28.37±3.20	29.9 ± 3.6 vs. 29.2 ± 3.5	29.4 ± 3.7 vs. 27.4 ± 6.0	29.0 ± 5.1 vs. 30.2 ± 5.2	27.8 ± 3.7 vs. 27.7 ± 3.9
Pituitary suppression	GnRH- agonist long protocol Buserelin	GnRH-agonist long protocol 0.5 mg/d Buserelin	GnRH-agonist long protocol 0.1 mg	leuprolide acetate	GnRH-agonist long protocol 0.1 mg of subcutaneous triptorelin
Follicle Stimulation	HMG	rFSH	HMG	rFSH	HMG
comparison	Cabergoline vs. Coasting	Cabergoline vs. Coasting	Cabergoline vs. Coasting vs. step-down	Cabergoline vs. Coasting	Cabergoline vs. Coasting vs. coastng with cabergoline
Triggering	HCG (10,000 IU)	HCG (10,000 IU)	HCG (10,000 IU)	HCG	HCG (10,000 IU)
intervention	0.5 mg/d cabergoline for 8 days starting on day of hCG.	0.5 mg/d cabergoline for 7 days starting on day of hCG.	0.5 mg/d cabergoline for 8 days starting on day of hCG.	0.5 mg/d cabergoline for 8 days starting on day of hCG.	0.25 mg/d cabergoline for 8 days starting on day of hCG.
comparator	Coasting	Coasting	Coasting	Coasting	Coasting
RCT	Yes	Yes	Yes	Yes	Yes
Clinical pregnancy definition	The presence of gestational sac or cardiac activity 3 weeks after ET.	Sonographic detection of the gestational sac was confirmed.	A gestational sac or cardiac pulsation 3 weeks after ET.	Intrauterine gestational sac by transvaginal ultrasonography.	Visible intrauterine gestational sac on transvaginal ultrasonography.
Authors' conclusions	Cabergoline was as effective as coasting in the prevention of early severe OHSS in high risk patients, but yielded more retrieved oocytes.	Cabergoline seems to be an effective, convenient, and safe drug for the prevention of OHSS.	Coasting may have a higher pregnancy rate and higher preventive method.	Cabergoline was effective to reduce moderate-severe OHSS without sacrificing pregnancy rates in patients at risk of developing OHSS	Combining coasting and cabergoline was associated with a lower OHSS rate compared with either therapy alone.

Continued

inclusion criteria	≥20 follicles in both ovaries, most of follicles were >15 mm and at least 3 follicles> 18 mm.	≥20 follicles in both ovaries, the majority being ≥14 mm in diameter, and E_2 > 3000 pg/mL.	≥20 follicles in both ovaries, or most of follicles were >15 mm, ≤35 years old, PCOS Patients.	E_2 ≥ 3500 pg/mL; used cabergoline or coasting for OHSS prevention.	≥15 oocytes collected on ovum pickup day, 20 - 35 years, BMI is up to 30, E_2 ≥ 3500 pg/mL on the day of hCG administration.
Exclusion criteria	who did have a tendency to cancel their cycle	Participants in whom the use of dopamine agonists were contraindicated	No stated	No stated	Infertility that was due to male and uterine factors.

HMG = human menopausal gonadotropin, rFSH = recombinant follicle stimulating hormone, HCG = human choionic gonadotophin, RCT = randomized controlled trial.

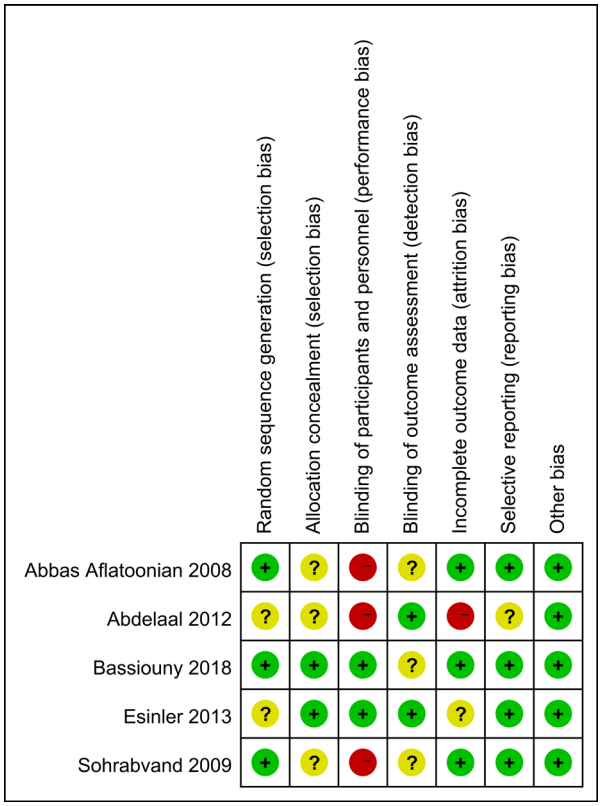


Figure 2. Quality assesssments of included studies. ? = unclear, + = low risk, − = high risk.

3.3.2. Implantation Rate

Three studies of included in this meta-analysis reported implantation rate (Figure 3(b)). The results displayed there was no significant difference between the two groups in implantation rate (RR 1.00, 95% CI 0.75 - 1.32; P = 0.97). No heterogeneity between studies (I^2 = 0).

3.3.3. The Incidence of OHSS

The incidence of OHSS was reported in 5 articles (Figure 3(c)). Pooling their results showed that there was no significant difference in the incidence of OHSS between the two groups (RR 0.93, 95% CI 0.38 - 2.31; P = 0.88). There was no heterogeneity between articles (I^2 = 0).

3.3.4. Fertilization Rate

Only 3 pieces provided fertilization rate (**Figure 3(d)**). There was no significant difference in fertilization rate (SMD 0.70, 95% CI −0.10, 1.50; P = 0.09). While, there were high heterogeneity among the articles (I^2 = 88%), so subgroup analysis was conducted by the dose of cabergoline. It turns out there was a significant difference between cabergoline with 0.5 mg/d and coasting groups regarding the fertilization rate (SMD 1.08, 95% CI 0.66, 1.50; P < 0.001), and the cabergoline-treated group showed a higher fertilization rate with no heterogeneity (I^2 = 0). However, the other group under the treatment of 0.25 mg/d with cabergoline is of little significance (SMD 0.03, 95% CI −0.25, 0.31; P = 0.82).

3.3.5. Number of Oocytes Retrieved

Among the 5 articles included, 4 of them reported the number of oocytes retrieved (**Figure 3(e)**). The results showed that oocytes number increased significantly in the cabergoline group (SMD 0.80, 95% CI 0.30, 1.30, P = 0.002) with a high heterogeneity among the various articles (I^2 = 76%).

3.3.6. Number of Embryo Transfer

4 studies reported the number of embryo transfer, which were included in this meta-analysis (**Figure 3(f)**). The results demonstrated that no significant difference between the two groups in the number of embryo transfer (SMD −0.04, 95% CI −0.24, 0.17; P = 0.71) with no heterogeneity among these articles (I^2 = 0).

3.3.7. E_2 on HCG day

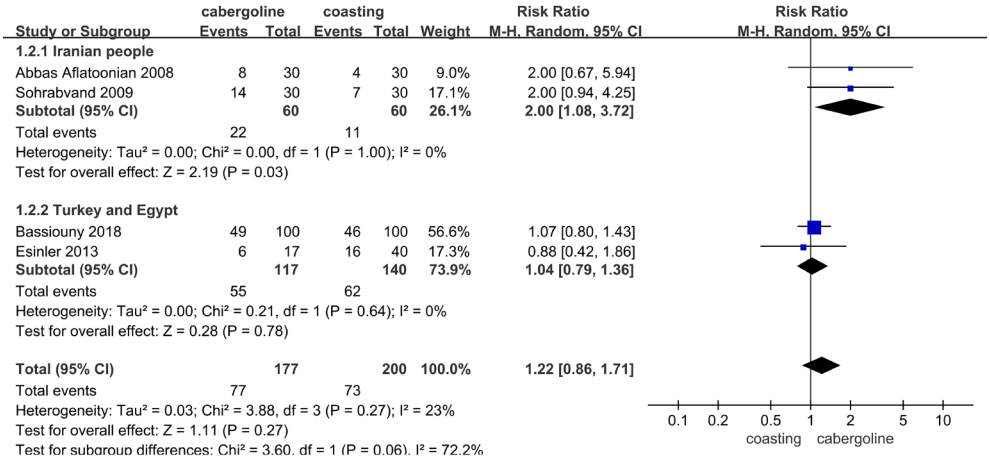
The E_2 level on the day of HCG injection was all reported in the 5 selected articles (**Figure 3(g)**). It showed that there was no significant difference in E_2 level between the two groups (SMD 0.21, 95% CI −0.25, 0.68; P = 0.37) with a high heterogeneity among the articles (I^2 = 78%).

3.3.8. Number of Metaphase II Oocytes

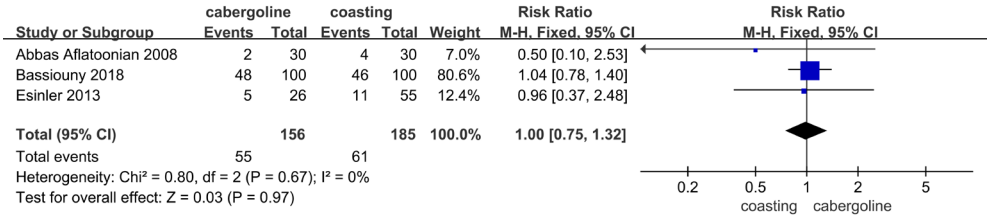
All 5 articles reported number of MII oocytes (**Figure 3(h)**). The results showed that oocytes number (SMD 0.71, 95% CI 0.32, 1.11, P < 0.001) increased significantly in the cabergoline group with a high heterogeneity among the various articles (I^2 = 69%).

3.3.9. Abortion Rate

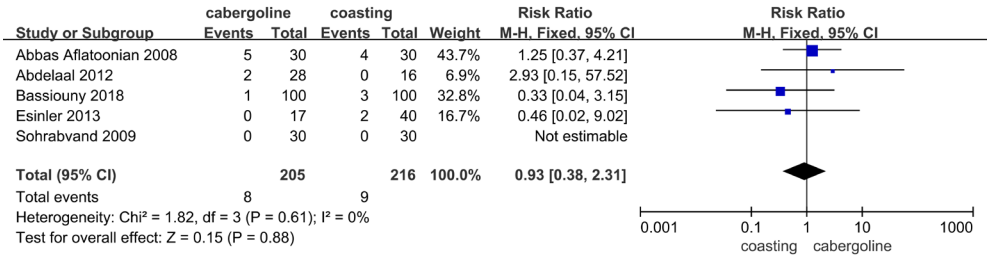
Three of five studies reported the abortion rate in this meta-analysis (**Figure 3(i)**). The final results showed that there is no statistically significant difference between the two groups (RR 0.61, 95% CI [0.21, 1.83], P = 0.38) with a significant heterogeneity character among these studies (I^2 = 54%). Subgroup analysis was performed according to the dosage of cabergoline. The pooled results indicated that the occurrence of abortion in coasting group is higher than in cabergoline group when the dose of cabergoline is in 0.5mg/d (RR 0.33, 95% CI [0.13, 0.83], P = 0.02) with no heterogeneity between articles (I^2 = 0%). Nevertheless, about the other group who under the treatment of 0.25 mg/d of cabergoline, there was no statistical significance when compared with coasting group (RR 1.33, 95% CI [0.48, 3.70], P = 0.58).


cabergoline coasting Risk Ratio Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI M-H, Random, 95% CI
1.2.1 Iranian people
Abbas Aflatoonian 2008 8 30 4 30 9.0% 2.00 [0.67, 5.94]
Sohrabvand 2009 14 30 7 30 17.1% 2.00 [0.94, 4.25]
Subtotal (95% CI) 60 60 26.1% 2.00 [1.08, 3.72]
Total events 22 11
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 1.00); I² = 0%
Test for overall effect: Z = 2.19 (P = 0.03)
1.2.2 Turkey and Egypt
Bassiouny 2018 49 100 46 100 56.6% 1.07 [0.80, 1.43]
Esinler 2013 6 17 16 40 17.3% 0.88 [0.42, 1.86]
Subtotal (95% CI) 117 140 73.9% 1.04 [0.79, 1.36]
Total events 55 62
Heterogeneity: Tau² = 0.00; Chi² = 0.21, df = 1 (P = 0.64); I² = 0%
Test for overall effect: Z = 0.28 (P = 0.78)
Total (95% CI) 177 200 100.0% 1.22 [0.86, 1.71]
Total events 77 73
Heterogeneity: Tau² = 0.03; Chi² = 3.88, df = 3 (P = 0.27); I² = 23%
Test for overall effect: Z = 1.11 (P = 0.27)
Test for subgroup differences: Chi² = 3.60, df = 1 (P = 0.06), I² = 72.2%
0.1 0.2 0.5 1 2 5 10
coasting cabergoline

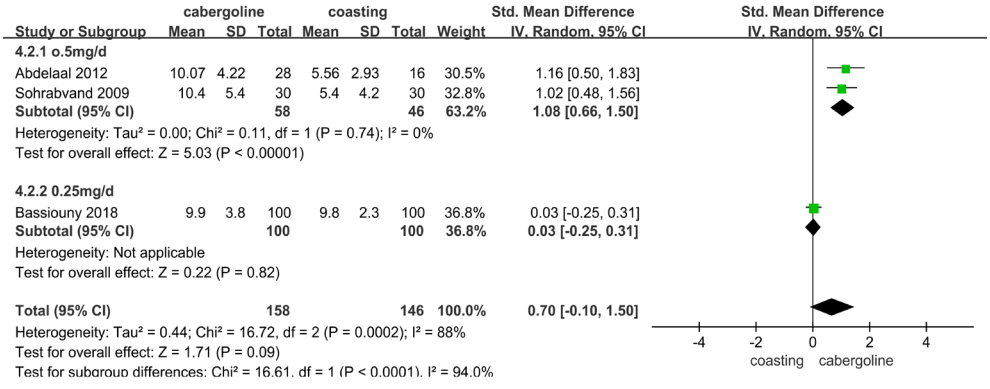
(a)


cabergoline coasting Risk Ratio Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI M-H, Fixed, 95% CI
Abbas Aflatoonian 2008 2 30 4 30 7.0% 0.50 [0.10, 2.53]
Bassiouny 2018 48 100 46 100 80.6% 1.04 [0.78, 1.40]
Esinler 2013 5 26 11 55 12.4% 0.96 [0.37, 2.48]
Total (95% CI) 156 185 100.0% 1.00 [0.75, 1.32]
Total events 55 61
Heterogeneity: Chi² = 0.80, df = 2 (P = 0.67); I² = 0%
Test for overall effect: Z = 0.03 (P = 0.97)
0.2 0.5 1 2 5
coasting cabergoline

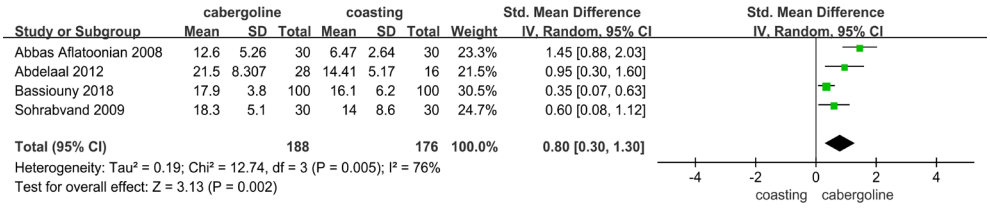
(b)


cabergoline coasting Risk Ratio Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI M-H, Fixed, 95% CI
Abbas Aflatoonian 2008 5 30 4 30 43.7% 1.25 [0.37, 4.21]
Abdelaal 2012 2 28 0 16 6.9% 2.93 [0.15, 57.52]
Bassiouny 2018 1 100 3 100 32.8% 0.33 [0.04, 3.15]
Esinler 2013 0 17 2 40 16.7% 0.46 [0.02, 9.02]
Sohrabvand 2009 0 30 0 30 Not estimable
Total (95% CI) 205 216 100.0% 0.93 [0.38, 2.31]
Total events 8 9
Heterogeneity: Chi² = 1.82, df = 3 (P = 0.61); I² = 0%
Test for overall effect: Z = 0.15 (P = 0.88)
0.001 0.1 1 10 1000
coasting cabergoline

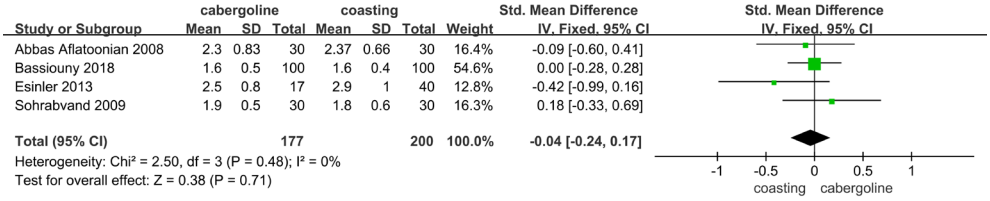
(c)


cabergoline coasting Std. Mean Difference Std. Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI IV, Random, 95% CI
4.2.1 o.5mg/d
Abdelaal 2012 10.07 4.22 28 5.56 2.93 16 30.5% 1.16 [0.50, 1.83]
Sohrabvand 2009 10.4 5.4 30 5.4 4.2 30 32.8% 1.02 [0.48, 1.56]
Subtotal (95% CI) 58 46 63.2% 1.08 [0.66, 1.50]
Heterogeneity: Tau² = 0.00; Chi² = 0.11, df = 1 (P = 0.74); I² = 0%
Test for overall effect: Z = 5.03 (P < 0.00001)
4.2.2 0.25mg/d
Bassiouny 2018 9.9 3.8 100 9.8 2.3 100 36.8% 0.03 [-0.25, 0.31]
Subtotal (95% CI) 100 100 36.8% 0.03 [-0.25, 0.31]
Heterogeneity: Not applicable
Test for overall effect: Z = 0.22 (P = 0.82)
Total (95% CI) 158 146 100.0% 0.70 [-0.10, 1.50]
Heterogeneity: Tau² = 0.44; Chi² = 16.72, df = 2 (P = 0.0002); I² = 88%
Test for overall effect: Z = 1.71 (P = 0.09)
Test for subgroup differences: Chi² = 16.61, df = 1 (P < 0.0001), I² = 94.0%
-4 -2 0 2 4
coasting cabergoline

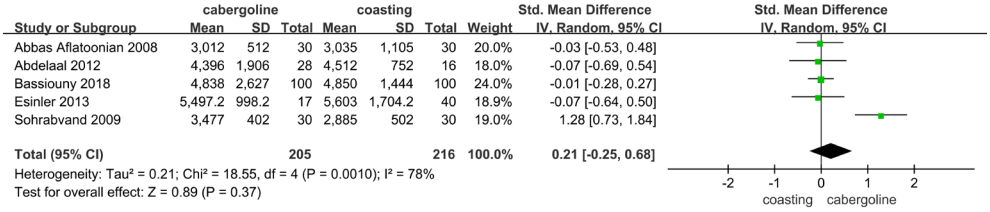
(d)


cabergoline coasting Std. Mean Difference Std. Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI IV, Random, 95% CI
Abbas Aflatoonian 2008 12.6 5.26 30 6.47 2.64 30 23.3% 1.45 [0.88, 2.03]
Abdelaal 2012 21.5 8.307 28 14.41 5.17 16 21.5% 0.95 [0.30, 1.60]
Bassiouny 2018 17.9 3.8 100 16.1 6.2 100 30.5% 0.35 [0.07, 0.63]
Sohrabvand 2009 18.3 5.1 30 14 8.6 30 24.7% 0.60 [0.08, 1.12]
Total (95% CI) 188 176 100.0% 0.80 [0.30, 1.30]
Heterogeneity: Tau² = 0.19; Chi² = 12.74, df = 3 (P = 0.005); I² = 76%
Test for overall effect: Z = 3.13 (P = 0.002)
-4 -2 0 2 4
coasting cabergoline

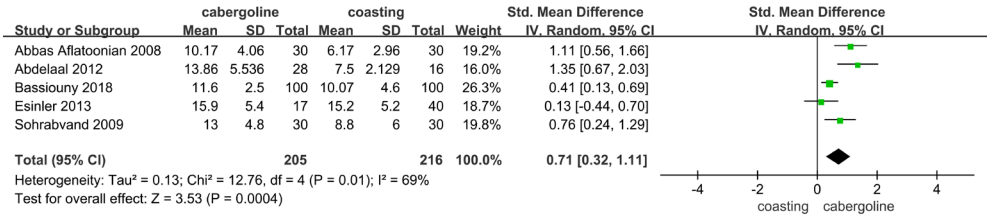
(e)


cabergoline
coasting
Std. Mean Difference
Std. Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Fixed, 95% CI
IV, Fixed, 95% CI
Abbas Aflatoonian 2008 2.3 0.83 30 2.37 0.66 30 16.4% -0.09 [-0.60, 0.41]
Bassiouny 2018 1.6 0.5 100 1.6 0.4 100 54.6% 0.00 [-0.28, 0.28]
Esinler 2013 2.5 0.8 17 2.9 1 40 12.8% -0.42 [-0.99, 0.16]
Sohrabvand 2009 1.9 0.5 30 1.8 0.6 30 16.3% 0.18 [-0.33, 0.69]
Total (95% CI) 177 200 100.0% -0.04 [-0.24, 0.17]
Heterogeneity: Chi² = 2.50, df = 3 (P = 0.48); I² = 0%
Test for overall effect: Z = 0.38 (P = 0.71)
-1 -0.5 0 0.5 1
coasting cabergoline

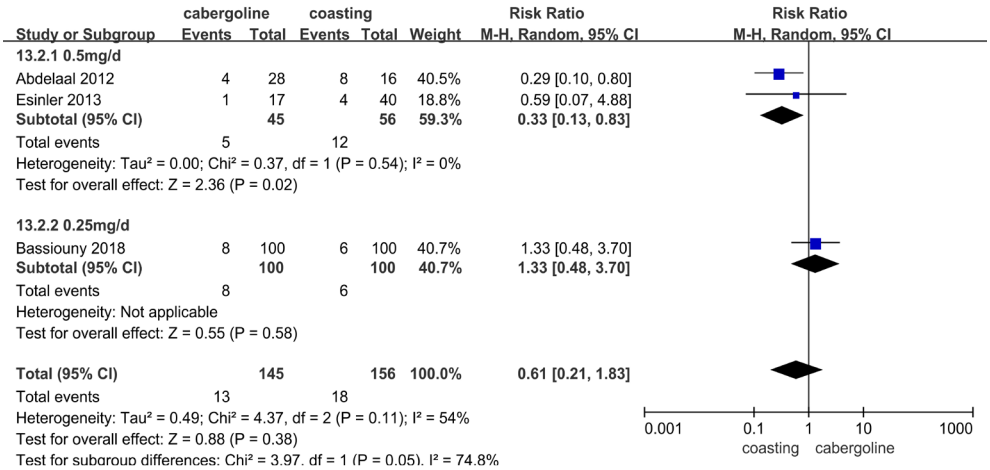
(f)


cabergoline
coasting
Std. Mean Difference
Std. Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
Abbas Aflatoonian 2008 3,012 512 30 3,035 1,105 30 20.0% -0.03 [-0.53, 0.48]
Abdelaal 2012 4,396 1,906 28 4,512 752 16 18.0% -0.07 [-0.69, 0.54]
Bassiouny 2018 4,838 2,627 100 4,850 1,444 100 24.0% -0.01 [-0.28, 0.27]
Esinler 2013 5,497.2 998.2 17 5,603 1,704.2 40 18.9% -0.07 [-0.64, 0.50]
Sohrabvand 2009 3,477 402 30 2,885 502 30 19.0% 1.28 [0.73, 1.84]
Total (95% CI) 205 216 100.0% 0.21 [-0.25, 0.68]
Heterogeneity: Tau² = 0.21; Chi² = 18.55, df = 4 (P = 0.0010); I² = 78%
Test for overall effect: Z = 0.89 (P = 0.37)
-2 -1 0 1 2
coasting cabergoline

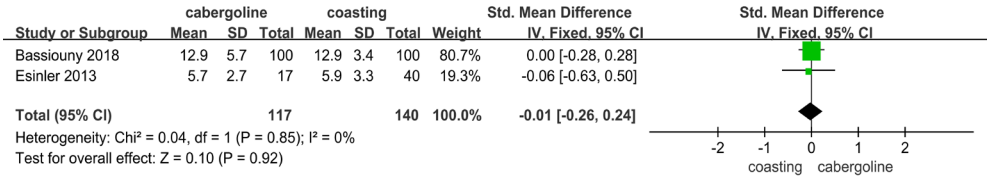
(g)


cabergoline
coasting
Std. Mean Difference
Std. Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
Abbas Aflatoonian 2008 10.17 4.06 30 6.17 2.96 30 19.2% 1.11 [0.56, 1.66]
Abdelaal 2012 13.86 5.536 28 7.5 2.129 16 16.0% 1.35 [0.67, 2.03]
Bassiouny 2018 11.6 2.5 100 10.07 4.6 100 26.3% 0.41 [0.13, 0.69]
Esinler 2013 15.9 5.4 17 15.2 5.2 40 18.7% 0.13 [-0.44, 0.70]
Sohrabvand 2009 13 4.8 30 8.8 6 30 19.8% 0.76 [0.24, 1.29]
Total (95% CI) 205 216 100.0% 0.71 [0.32, 1.11]
Heterogeneity: Tau² = 0.13; Chi² = 12.76, df = 4 (P = 0.01); I² = 69%
Test for overall effect: Z = 3.53 (P = 0.0004)
-4 -2 0 2 4
coasting cabergoline

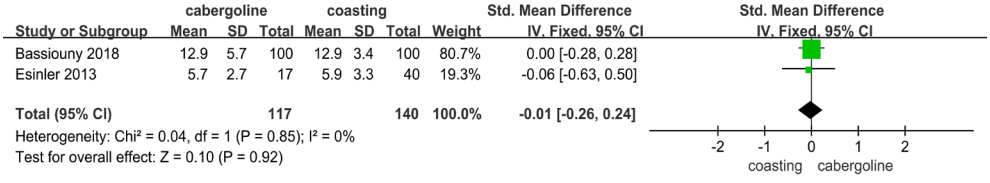
(h)


cabergoline
coasting
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
13.2.1 0.5mg/d
Abdelaal 2012 4 28 8 16 40.5% 0.29 [0.10, 0.80]
Esinler 2013 1 17 4 40 18.8% 0.59 [0.07, 4.88]
Subtotal (95% CI) 45 56 59.3% 0.33 [0.13, 0.83]
Total events 5 12
Heterogeneity: Tau² = 0.00; Chi² = 0.37, df = 1 (P = 0.54); I² = 0%
Test for overall effect: Z = 2.36 (P = 0.02)
13.2.2 0.25mg/d
Bassiouny 2018 8 100 6 100 40.7% 1.33 [0.48, 3.70]
Subtotal (95% CI) 100 100 40.7% 1.33 [0.48, 3.70]
Total events 8 6
Heterogeneity: Not applicable
Test for overall effect: Z = 0.55 (P = 0.58)
Total (95% CI) 145 156 100.0% 0.61 [0.21, 1.83]
Total events 13 18
Heterogeneity: Tau² = 0.49; Chi² = 4.37, df = 2 (P = 0.11); I² = 54%
Test for overall effect: Z = 0.88 (P = 0.38)
Test for subgroup differences: Chi² = 3.97, df = 1 (P = 0.05), I² = 74.8%
0.001 0.1 1 10 1000
coasting cabergoline

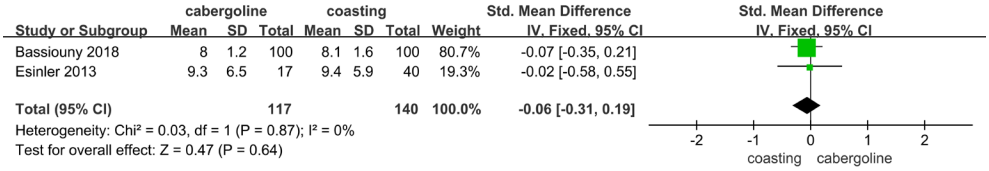
(i)


cabergoline
coasting
Std. Mean Difference
Std. Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Fixed, 95% CI
IV, Fixed, 95% CI
Bassiouny 2018 12.9 5.7 100 12.9 3.4 100 80.7% 0.00 [-0.28, 0.28]
Esinler 2013 5.7 2.7 17 5.9 3.3 40 19.3% -0.06 [-0.63, 0.50]
Total (95% CI) 117 140 100.0% -0.01 [-0.26, 0.24]
Heterogeneity: Chi² = 0.04, df = 1 (P = 0.85); I² = 0%
Test for overall effect: Z = 0.10 (P = 0.92)
-2 -1 0 1 2
coasting cabergoline

(j1)


cabergoline
coasting
Std. Mean Difference
Std. Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Fixed, 95% CI
IV, Fixed, 95% CI
Bassiouny 2018 12.9 5.7 100 12.9 3.4 100 80.7% 0.00 [-0.28, 0.28]
Esinler 2013 5.7 2.7 17 5.9 3.3 40 19.3% -0.06 [-0.63, 0.50]
Total (95% CI) 117 140 100.0% -0.01 [-0.26, 0.24]
Heterogeneity: Chi² = 0.04, df = 1 (P = 0.85); I² = 0%
Test for overall effect: Z = 0.10 (P = 0.92)
-2 -1 0 1 2
coasting cabergoline

(j2)



(j3)

Figure 3. Forest plots for rate of (a) pregnancy rate, (b) implantation rate, (c) the incidence of OHSS, (d) fertilization rate, (e) number of oocytes retrieved (f) number of embryo transfer, (g) E_2 on HCG day, (h) number of metaphase II oocytes, (i) abortion rate, (j1, j2, j3) number of follicles > 17 mm, 15 - 17 mm, 10 - 14 mm on day of HCG.

3.3.10. Number of Follicles > 17 mm, 15 - 17 mm, 10 - 14 mm on Day of HCG

Totally five articles were involved in the meta-analysis, while only 2 articles reported number of follicles > 17 mm, 15 - 17 mm, 10 - 14 mm on day of HCG (**Figure 3(j)**). It demonstrated that there was no significant difference in the number of follicles between the two treatment groups, regardless of the follicular diameter (SMD −0.01, 95% CI −0.26, 0.24; P = 0.92) (SMD −0.08, 95% CI −0.33, 0.17; P = 0.53) (SMD −0.06, 95% CI −0.31, 0.19; P = 0.64). No heterogeneity exist between articles ($I^2 = 0$).

4. Discussion

This meta-analysis showed that in the process of assisted reproductive treatment who were at high-risk of OHSS patients received preventive treatment of "cabergoline" and "coasting". The conclusion is both two methods were all effective in preventing OHSS.

In this meta-analysis, we compared the effectiveness of two methods with cabergoline or coasting on the prevention of OHSS and the effectiveness on IVF-ET or ICSI-ET outcomes with high ovarian responders with FSH or HCG. It turns out no significant difference in the rate of implantation, E_2 level and number of follicles on the day of HCG injection, and number of embryo transfer between two groups. But in cabergoline group, there were more oocytes and MII oocytes, and higher rate of fertilization and clinical pregnancy. In the coasting group, a higher abortion rate was observed. Subgroup analysis result showed that 0.5 mg cabergoline daily was obviously increased fertilization rate and the abortion rate was significantly lower than coasting group. One study proved that the combined administration provided better protection without notable side effects [18]. However, Hwang [19] pointed out that the efficacy of cabergoline is not good in preventing severe OHSS through two cases.

A previous research showed that dopamine agonist is the first pathophysiological method for preventing or minimizing OHSS without affecting pregnancy outcome [20]. Furthermore, the dosing of cabergoline or coasting can effectively prevent mild to moderate OHSS [21] [22] [23] [24]. While multiple studies have shown that coasting does not unfavorably affect on the function and number of mature oocytes, quality of embryo, endometrial receptivity and number of implan-

tation in the prevention of severe OHSS [25] [26] [27] [28] [29]. The number of oocytes in coasting group was significantly lower than that in other treatment groups [30]. Mahvash [31] reported that the effect of cabergoline in 0.5 mg/d is superior to every two days in preventing OHSS compared with 0.25 mg/d cabergoline. Vascular heart disease should be taken into consideration when under the treatment of cabergoline, especially in a higher dosage [32]. Isaza [33] found that if treatment of coasting is prolonged for more than 4 days, there is a significantly decreased in the rate of implantation and the rate of pregnancy. Whilst there was still not high-quality evidence to identify that coasting was superior to other treatment, and there is too few data to determine whether there is any difference results between two groups [34].

Our research is the first meta-analysis to compare the safety and effectiveness of cabergoline and coasting in the prevention of OHSS. One of the advantages of this study is the integration of multi-country and multi-center data.

5. Conclusion

The effect of cabergoline and coasting in preventing severe OHSS is quite similar. Simultaneously, it was demonstrated that the patients given cabergoline in a daily dose of 0.5 mg, the effect can also increase significantly in the number of oocytes retrieved, the number of MII oocytes, fertilization rate but decrease the abortion rate.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Abbreviations

OHSS: ovarian hyperstimulation syndrome

IVF: *in vitro* fertilization

ICSI: intracytoplasmic sperm injection

E_2: estradiol

MII: metaphase II

RR: risk ratio

rFSH: Recombinant follicle-stimulating hormone

SMD: Std. Mean Differences