Can dopamine agonists reduce the incidence and severity of OHSS in IVF/ICSI treatment cycles? A systematic review and meta-analysis

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BACKGROUND: Recently, dopamine agonists were proposed as a prophylactic treatment for ovarian hyperstimulation syndrome (OHSS) in women at high risk in IVF/ICSI treatment cycles.

METHODS: We conducted a systematic review and meta-analysis of randomized trials comparing the prophylactic effect of the dopamine agonist, cabergoline, versus no treatment in IVF/ICSI cycles. Primary outcome was OHSS incidence per randomized woman. Secondary outcomes were live birth rate, ongoing pregnancy rate, clinical pregnancy rate and miscarriage rate. Searches (until September 2009) were conducted in MEDLINE, EMBASE, Science Direct, Cochrane Library and databases of abstracts.

RESULTS: Four randomized trials entailing 570 women were included. There was evidence of a statistically significant reduction in the incidence of OHSS in the cabergoline group (OR 0.41, 95% CI 0.25–0.66) with an absolute risk reduction of 12% (95% CI 6.1–18.2%), but there was no statistically significant evidence of a reduction in severe OHSS (OR 0.50, 95% CI 0.20–1.26). There was no evidence for a difference in clinical pregnancy rate (OR 1.07, 95% CI 0.70–1.62) and miscarriage rate (OR 0.31, 95% CI 0.03–3.07).

CONCLUSION: Prophylactic treatment with the dopamine agonist, cabergoline, reduces the incidence, but not the severity of OHSS, without compromising pregnancy outcomes.

Key words: OHSS / dopamine agonist / cabergoline / meta-analysis / IVF and ICSI
Introduction

Ovarian hyperstimulation syndrome (OHSS) is an iatrogenic, serious and potentially fatal complication of ovarian stimulation, affecting 1–14% of all IVF/ICSI cycles (Pellicer and Garcia-Velasco, 2003). OHSS may be associated with massive ovarian enlargement, ascites, hydrothorax, liver dysfunction and renal failure and can lead to cancellation of an IVF cycle, prolonged bed rest or hospitalization, all of which have significant emotional, social and economic consequences (Delwayne et al., 2002; Engmann et al., 2008). Many strategies have been tried to prevent OHSS, including cycle cancellation, coasting (Garcia-Velasco et al., 2006), intravenous albumin administration around the time of oocyte retrieval (Abouelghar et al., 2002, 2009), GnRH agonist as an oocyte trigger in GnRH antagonist cycles (Kol and Solt, 2008; Youssef et al., 2009), natural-cycle IVF (Edwards, 2007) or in vitro oocyte maturation (Loutridis et al., 2006). Unfortunately, none of the strategies currently employed completely prevents OHSS after HCG administration.

OHSS can present in an early form which is related to the ovarian response and exogenous human chorionic gonadotrophin (HCG) administration, and is detected 3–9 days after HCG administration, and a late form which is due to endogenous HCG and is diagnosed 10–17 days later (Mathur and Jenkins, 2000). Besides HCG, there are certain vasoactive substances such as vascular endothelial growth factor (VEGF) that also play a role in the development of OHSS (Yan et al., 1993; Rizk et al., 1997; Enskog et al., 2001; Soares et al., 2008).

A potential new strategy to prevent OHSS and reduce the severity is the use of a dopamine agonist (Papaleo et al., 2001; Knoepfelmacher, 2006). It was observed that the administration of a dopamine agonist in immature rats at low doses simultaneously with HCG prevented an increase in vascular permeability and did not affect angiogenesis (Gomez et al., 2006); the effect was due to the availability of dopamine type 2 receptors (Alvarez et al., 2007a).

A number of clinical trials have recently tested the clinical usefulness of a dopamine agonist as a possible way to reduce the occurrence and severity of OHSS (Alvarez et al., 2007a, b; Papaleo et al., 2001; Manno et al., 2006). The objective of our systematic review and meta-analysis was to determine whether a dopamine agonist can indeed reduce the occurrence and severity of OHSS syndrome in high-risk patients undergoing ovarian hyperstimulation in IVF/ICSI treatment cycles.

Methods

Search strategy for identification of studies

The following electronic databases were searched: MEDLINE, EMBASE, Science Direct, Cochrane Central Register of Controlled Trials (CENTRAL) and Web of Science. National Research Register (NRR), a register of ongoing trials, and the Medical Research Council’s Clinical Trials Register A search strategy was carried out based on the following terms: OHSS, Dopamine agonist, cabergoline, AND ovarian hyperstimulation syndrome chorionic or OHSS AND IVF/ICSI/ART AND randomized controlled trial(s) OR randomised controlled trial(s). Furthermore, we examined the reference lists of all known primary studies, review articles, citation lists of relevant publications and abstracts of major scientific meetings (e.g. ESHRE and ASRM) and included studies to identify additional relevant citations. Finally, the review authors sought ongoing and unpublished trials by contacting experts in the field. In addition, references from all identified articles were checked, and hand searches of the abstracts from the annual meetings of the American Society for Reproductive Medicine and the European Society for Human Reproduction and Embryology were performed. If necessary, additional information was sought from the authors. The search was not restricted by language. The searches were conducted independently by M.Y, M.H and M.W.

Study selection and data extraction

Studies were selected if the target population was infertile couples, of any cause, having a high risk of developing OHSS. The therapeutic interventions were dopamine agonist for the prevention of OHSS in IVF or ICSI treatment. Studies had to be of randomized, controlled design. The primary outcome measure of interest was the reduction of moderate-to-severe OHSS incidence per randomized woman.

Studies were selected in a two-stage process. First, the titles and abstracts from the electronic searches were scrutinized by three reviewers independently (M.A.F.M.Y, M.A.H. and M.W.) and full manuscripts of all citations that were likely to meet the predefined selection criteria were obtained. Secondly, final inclusion or exclusion decisions were made on examination of the full manuscripts. Any disagreements about inclusion were resolved by consensus or arbitration by a third reviewer (F.V., M.M, S.K. and H.G.A.). The selected studies were assessed for methodological quality by using the components of study design that are related to internal validity (Juni et al., 2001). Information on the adequacy of randomization, concealment and blinding was extracted. When needed, the reviewers wrote to the authors and obtain extra information and the raw data. From each study, outcome data were extracted in 2 × 2 tables. Data extraction was performed in duplicate by M.Y, M.H and M.W.

Definition of outcome measures

The outcomes we planned to assess in our analysis were OHSS incidence, OHSS severity and onset of OHSS, live birth rate, ongoing pregnancy rate, clinical pregnancy rate and miscarriage rate. The severity of OHSS in the four studies was determined using; Rizk and Abouelghar 2003 classification (Carizza et al., 2008), modified Golan et al. 1989 classification (Alvarez et al., 2007a) and Golan et al. 1989 (Shaltout et al., 2009) and Navot et al.’s classification (Salah Edeen et al., 2009). The OHSS incidence, live birth rate, ongoing pregnancy rate, clinical pregnancy rate and miscarriage rate were calculated based on the number of patients randomized in all studies even if some patients were excluded or dropped out after randomization.

Statistical analysis

Dichotomous outcomes were expressed as an odds ratio (OR) with 95% CI using a fixed effects model (Mantel and Haenszel, 1959). For the primary outcome, OHSS incidence, the absolute risk reduction (ARR) and the number needed to treat (NNT) were also presented. Heterogeneity of treatment effects was evaluated graphically using forest plots (Lewis and Clarke, 2001) and statistically using the Breslow and Day χ² test. Subgroup analyses according to the severity and time of onset of OHSS were performed. All statistical analyses were performed using RevMan 5.0 (Cochrane Collaboration, Oxford, UK).

Results

The search strategy yielded 17 publications related to the topic. Thirteen publications were excluded as they did not fulfil the selection criteria (Fig. 1). The excluded trials with the main reason for exclusion are shown in Table I. The included four trials enrolled, in total, 570
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Two studies used computer-generated randomization (Alvarez et al., 2007a; Carizza et al., 2008). We contacted the authors to get extra information about the methodology quality of the studies and the outcomes (Alvarez et al., 2007a; Carizza et al., 2008; Salah Edeen et al., 2009; Shaltout et al., 2009). The studies were generally small and underpowered for the clinically relevant outcome of OHSS, with sample sizes varying from 82 to 200 patients. One study included donors (Alvarez et al., 2007a) and the other three studies included patients at high risk of OHSS. Only two trials were published as full papers (Alvarez et al., 2007a; Carizza et al., 2008) and the other two trials were abstracts presented at the ESHRE meeting in Amsterdam (Shaltout et al., 2009; Salah Edeen et al., 2009). Cabergoline was the dopamine agonist in all trials.

**OHSS incidence per woman randomized**

All trials reported on the OHSS incidence. The actual incidence varied from 12% to 50% in the control group and from 3% to 10% in the agonist group. Pooling the data resulted in a significantly lower OHSS incidence in the cabergoline group (OR 0.41; 95% CI 0.25–0.66) with an ARR following cabergoline of 12% (95% CI 6.1–18.2%) assuming an OHSS control rate of 25%. The corresponding NNT was 9 (95% CI 5.5–16.5). The heterogeneity tests were non-significant ($I^2 = 0%$ and $P = 0.74$), indicating that there was no statistical inconsistency between the four trials (Fig. 2).

**Severity of OHSS**

The severity of OHSS was clearly described in four papers and we could stratify the OHSS cases into a severe and a moderate group. We subsequently pooled the data in a subgroup analysis according to the severity of OHSS. The incidence of both severe and moderate OHSS was 50% lower in the dopamine agonist group. This difference was statistically significant for moderate OHSS (OR 0.38, 95% CI 0.22–0.68). As severe OHSS is more rare, a statistically significant difference could not be shown (OR 0.50, 95% CI 0.20–1.26) (Fig. 3).

**Onset of OHSS**

For one paper, we could not extract data on the onset of OHSS as this study was done in donor patients and the end of study assessment was scheduled 7–10 days after the last dose of cabergoline or placebo (Alvarez et al., 2007a). For the other three papers, we could stratify the OHSS cases into an early and a late onset group. We subsequently pooled the data in a subgroup analysis according to the onset of OHSS. There was a statistically significant lower incidence of early onset OHSS in the cabergoline group than in the control group (OR 0.10, 95% CI 0.03–0.33). However, we did not find any evidence of a significant difference in the incidence of late onset OHSS (OR 0.95, 95% CI 0.49–1.81) (Fig. 4).

**Pregnancy outcomes**

There was no evidence of a statistically significant difference in live birth rate (1 RCT: 19/100 versus 15/100, OR 1.33, 95% CI 0.63–2.79) and ongoing pregnancy rate (1 RCT: OR 0.88, 95% CI 0.43 to
### Table II Characteristics of randomized trials of cabergoline versus placebo/or no treatment

<table>
<thead>
<tr>
<th>Trial</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Quality features</th>
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<tr>
<td>Alveizer (2007)</td>
<td>82 oocyte donors, patients at risk of developing OHSS. Risk was defined by the development of 20–30 follicles larger than 12 mm in diameter and retrieval of more than 20 oocytes. There was no difference between the subjects in age, BMI, years of infertility or cause of infertility. 6 patients in the study group and 7 patients in the control group excluded after randomization because &lt;20 follicles retrieved. Coasting was an exclusion criterion.</td>
<td>Stimulation: long GnRH agonist + 150–300 IU/day of FSH or HMG. Study group: 0.5 mg cabergoline daily for 8 days from the day of HCG injection. Control group: no treatment.</td>
<td>OHSS incidence, early and late diagnosis of severity: modified Golan et al., 1989 classification, where moderate OHSS was defined when ascites is detected by ultrasound while severe OHSS is defined when a clinical signs/symptoms of ascites and/or hydrothorax and breathing difficulties or if there is an evidence of haemoconcentration, coagulopathy, renal or hepatic function impairment (modified Golan et al. 1989 classification).</td>
<td>Randomization: computer generated. Concealed: yes. Sample size: yes. Blinding: double blinded. ITT: no.</td>
</tr>
<tr>
<td>Carriza et al. (2008)</td>
<td>166 patients for IVF/ICSI, E2 &gt;4000 pg/ml, baseline characteristics were similar in both groups. Age: 34.0 versus 33.6 BMI 1.67 versus 1.66. E2: 4932.6 versus 4948.7, r FSH (75 iu): 28.0 VERSUS 29.0, Aspirated oocytes: 23.0 versus 21.4.</td>
<td>Stimulation: OCP+ long GnRH agonist + 150–300 IU r FSH. Study group: 0.5 mg cabergoline daily for 3 weeks from the day after oocyte retrieval. Control group: no treatment. Both groups: received 20 g routine i.v. albumin on the day of oocyte retrieval. Follow-up: haematological tests and ultrasound every 48 h.</td>
<td>OHSS (early, late), implantation rate, clinical pregnancy rate, miscarriage rate. Diagnosis of severity: Rizk and Aboulghar (2003).</td>
<td>Randomization: computer generated. Concealed: yes. Sample size: yes. Blinding: no. ITT: unclear.</td>
</tr>
<tr>
<td>Salah Edeen and Alhelou (2009)</td>
<td>125 patients with PCOS, baseline characteristics were similar in both groups (data not given).</td>
<td>Long GnRH agonist protocol + 200–300 IU r FSH. Study group: 0.5 mg cabergoline oral on 2 successive days and repeated after 1 week starting from the day of HCG injection. Control group: no treatment. Follow-up: 5 days after HCG injection for clinical and sonographic assessment.</td>
<td>OHSS; severe OHSS is defined according to Navot et al. classification.</td>
<td>Randomization: closed envelopes. Concealed: unclear. Sample size: no. Blinding: no. ITT: unclear.</td>
</tr>
<tr>
<td>Shaltout et al. (2009)</td>
<td>200 women undergoing ICSI and at high risk for OHSS. OHSS risk was defined by E &gt;3500 pg/ml on HCG day plus 20 follicles &gt;10 mm baseline characteristics were similar between both groups (data not given). Patients with E2 &gt;5000 pg/ml were excluded.</td>
<td>Long GnRH agonist plus HMG plus 5000 IU HCG. Study group: 0.25 mg cabergoline daily for 8 days from the day of HCG injection. Control group: no treatment. Follow-up: haemoconcentration, ascites, ovarian volume.</td>
<td>OHSS incidence, severity and onset, fertilization rate, clinical pregnancy rate, number of retrieved oocytes, M2 number severe OHSS is defined according to Golan et al. (1989).</td>
<td>Randomization: closed envelopes. Concealed: unclear. Sample size: unclear. Blinding: no. ITT: yes.</td>
</tr>
</tbody>
</table>
1.78) (Shaltout et al., 2009). From two studies, data on clinical pregnancy rates could be extracted (Carizza et al., 2008; Shaltout et al., 2009). There was no evidence of a difference in clinical pregnancy rate between both groups (77/183 versus 73/180; OR 1.07, 95% CI 0.70–1.62; $I^2 = 0\%$). Two studies reported the miscarriage rate (Carizza et al., 2008; Shaltout et al., 2009). There was no evidence of statistical difference in miscarriage rate (2 RCT, 6/183 versus 8/183: OR 0.85, 95% CI 0.39–1.86).

**Discussion**

In this systematic review and meta-analysis of randomized trials, we showed that cabergoline significantly reduces the chance of developing OHSS in IVF and ICSI cycles. The corresponding NNT was nine (95% CI 5.5–16.5) with an ARR of 12%, 95% CI 6.1–18.2% following cabergoline use assuming an OHSS control rate of 25%. This means that you must treat nine patients with dopamine agonist to prevent one case of OHSS that would have happened otherwise. Subgroup analyses were underpowered to detect differences as only a few studies were included in the review. Furthermore, the clinically most relevant outcome, severe OHSS, has a low incidence. To show a statistical difference in severe OHSS more, preferably larger trials are needed. However, the data tend to suggest that cabergoline reduces the risk of both moderate and severe OHSS. There was also no evidence of statistically significant differences in live birth rate, ongoing pregnancy rate, clinical pregnancy rate and miscarriage rate in both groups.

There was clinical heterogeneity between trials in the dose of cabergoline either 0.5 mg oral or 0.25 mg oral and in the regimens used: (i) 0.5 mg oral cabergoline per day for 3 weeks beginning on the day after oocyte retrieval (Carriza et al., 2008); (ii) one 0.5 mg tablet of cabergoline daily for 8 days (Alveizer et al., 2007); (iii) 0.5 mg, one tablet on two successive days, repeated 1 week later, starting from day of HCG injection (Salah Edeen et al., 2009); (iv) cabergoline 0.25 mg daily for 8 days (Shaltout et al., 2009). This heterogeneity may generate misleading results. Only in one study were the outcome assessor and the patients blinded to the intervention group (Alvarez et al., 2007a), which might be a potential source of bias that could have yielded exaggerated estimates of the effect of cabergoline. However, the results were consistent across the trials and the results remained unaltered when a random-effect meta-analysis was conducted as sensitivity analysis.
Other non-randomized trials have also found that a dopamine agonist could be a useful treatment of OHSS. One trial showed an improvement in 20 hospitalized patients at risk of OHSS when starting the evening after oocyte retrieval and in 10 severely hyperstimulated pregnant women after 24–48 h of cabergoline administration at a dose of 1 mg every 48 h (Manno et al., 2005). In another non-randomized trial, doxapramine was used in 27 OHSS patients and 20 (74.1%) had satisfactory effects on diuresis and recovered from their clinical symptoms of OHSS (Ferraretti et al., 1992; Tsunoda et al., 2003).

There is concern about the effect of cabergoline on endometrial angiogenesis and its impact on implantation and miscarriage rates. In addition, there is a lack of reliable evidence on long-term effects on the babies born and general lack of safety data. In the included studies in our review, there was no difference in clinical pregnancy rates and miscarriage rates between the groups which may mean that endometrial angiogenesis is not affected. Also, two of the included RCTs followed the women up to the end of pregnancy and found no difference in the live birth rate between both treatment groups (Carizza et al., 2008; Shaltout et al., 2009; Novella-Maestre et al., 2009).

As far as we know, there are three non-randomized studies that did evaluate the long-term effects of cabergoline. The first was a case series of 226 pregnancies occurring in 205 women who had been exposed to cabergoline. Follow-up was available for 204 pregnancies. There were 24 miscarriages and three induced abortions because of major malformations (one Down syndrome in a 42-year-old woman, one limb-body wall complex, one hydrocephalus). Two of the 148 single live born infants had significant malformations: one mega-ureter and one scaphocephaly. The author concluded that there was no increase in miscarriage rate, that the distribution of birth-weights and sex ratio was within the expected range and that there was no increased rate of congenital malformations (Robert et al., 1996). The second study collected data on 61 pregnancies in 50 women who had been treated with cabergoline for hyperprolactinaemia. These pregnancies resulted in 12 (19.7%) early terminations (five induced abortions, six spontaneous miscarriages, one hydatidiform mole) and 49 (80.3%) live births. In one case, malformations were suspected on ultrasound at 12 gestational weeks and the pregnancy was terminated. There was one case of trisomy 18. The frequency of spontaneous and induced abortions and major congenital malformations was comparable with rates in the general population (Parazzini et al., 2002). The third study was retrospectively conducted as a pilot to evaluate the effect of cabergoline treatment on preventing OHSS in 35 women at a high risk of developing OHSS and who received cabergoline compared with high risk controls who did not receive cabergoline. Implantation rates were comparable between the groups (38.6% and 41.4%), and there were no differences in live births per cycle (40% in both groups). No minor or major malformation had been observed in any of the babies born (Alvarez et al., 2007b), but the sample size was too small to detect such a rare event.

Still there is a lack of reliable evidence on long-term effects of dopamine agonist on both treated women and babies born. Recently, concern was raised about the potential risks of new onset of cardiac valvulopathy with the use of dopamine agonists, especially cabergoline and pergolide in patients with Parkinson’s disease and requiring high doses for long duration (Schade et al., 2007; Zanettini et al., 2007). However, most studies of dopamine agonist use in prolactinoma where dopamine agonist doses are 10-fold lower than those employed in Parkinson’s disease have not observed valvular abnormalities (Cheung and Heaney, 2009; Herring et al., 2009). Furthermore, in a randomized trial, the long-term effect of cumulative doses of cabergoline was studied in patients with prolactinomas. In this trial, no correlation was found between the presence of significant heart-valve regurgitation and cabergoline cumulative dose, duration of cabergoline treatment, prior use of bromocriptine, age or prolactin levels. It was concluded that low doses of cabergoline seem to be a safe treatment of hyperprolactinaemic patients (Vallette et al., 2009). For OHSS, much lower doses are used over a shorter
period of time; hence the risk of cardiac valvulopathy is likely to be negligible.

Finally, it should not go unmentioned that the exact aetiology and pathogenesis of OHSS is still unclear, and therefore any preventive treatment remains non-specific. Further studies are needed to establish dose and protocol for OHSS prevention using dopamine agonists. Also, it would also be important to explore the use of other dopamine agonists.

There are many alternative protocols and medications to treat OHSS. In view of the low evidence, however, the role of dopamine agonists in the field of OHSS prevention is still unclear.

We conclude that dopamine agonist as a preventive treatment leads to a significantly lower OHSS incidence in high-risk patients, especially for early onset OHSS without compromising pregnancy outcomes.

Authors' roles

M.A.F.M.Y. initiated and conceptualized the protocol; to undertake data searching, selection of studies, data extraction, drafting of the review, assessment of studies for inclusion, interpretation and analysis of the data. Dr Carizza for providing information regarding methodology and the review. F.V., H.G.A., M.M. and S.K. took part in interpretation and analysis of the data, writing the review.

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