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REVIEW ARTICLE

Cabergoline for Ovarian Hyperstimulation: A Review of Clinical Evidence

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INTRODUCTION

Ovarian hyper stimulation syndrome (OHSS) is a potentially life-threatening situation. It is also considered to be most dangerous complication of assisted reproduction treatment (ART).[1]

It occurs where ovarian stimulation is done with gonadotrophins followed by administration of hCG to trigger the final steps of oocyte maturation.[5]

It is characterized by the presence of multiple leutinized cyst within the ovaries which leads to ovarian enlargement and secondary complications, such as increased capillary permeability and fluid shift to the third space.[1]

The incidence of OHSS in IVF cycles in which ovarian stimulation is performed using gonadotropins has been 0.5 to 2% whereas in intrauterine insemination cycles in which stimulation is performed with clomiphene citrate or aroamatase inhibitor, the condition is rarely seen.[8,13]

Recent studies have identified vascular endothelial growth factor as the major molecule responsible for increased capillary permeability.

Increased sensitivity to gonadotropin has been well documented in women with polycystic ovaries, of a young age, with low body mass index (BMI) and with history of allergies.[6,7,11]

The risk of OHSS increases with high serum E_2 levels and large number of ovarian follicles because the granulosa cells might secrete not only sex steroids but also the vasoactive substance responsible for OHSS.

Although, cytokines and growth factors (IL-2, IL-6, IL-8, IL-10 and 18), histamine, protactin, prostaglandin, and serum renin angiotension have been proposed in pathophysiology of OHSS, the exact responsible factors is under debate.[1]

On occasions OHSS may occur in the absence of exogenous gonadotropins administration in which cases the presence of endogenous hCG (Spontaneous pregnancy) is the only determination of hyper stimulation.[9,10]

Treatment of OHSS is generally conservative requiring costly long-term hospitalization, rendering prophylactic measures, a must.[2,3]

Cabergoline

Prophylactic administration of cabergoline, a dopamine agonist, is associated with a significant reduction in the incidence of symptoms and signs of moderate to severe OHSS. It inhibits, VEGFR-2 phosphorylation and signalling. Genetic variation may cause different responses in various populations, therefore, different responses to cabergoline may be detected.

Its use is not associated with an inferior ART outcomes or obstetric/neonatal complications.[2,4,5]

When and how to Start Cabergoline

For prevention of OHSS cabergoline is administered during controlled ovarian stimulation (with gonadotropins or other ovarian stimulating agents) prior to triggering final maturation/ovulation with, e.g. hCG. Preferably, administration is initiated during the last week of stimulation. Administration is continued for about 1 to 3 weeks after hCG stimulation for treatment of OHSS, administration of cabergoline is initiated once a patient has been diagnosed with moderate to severe OHSS (when signs and symptoms of OHSS first appear), at a dose of about 0.05 to 1 mg/day for about 1 to 28 days, preferably from about 7 to 14 days, or until symptoms abate.

Ibrahim Esinlear et al compared cabergoline with coasting to prevent moderate to severe ovarian hyperstimulation symptoms. Implantation rate, clinical pregnancy, per embryo transfer and miscarriages rates were not different between the two groups. There was no OHSS

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in the cabergoline group (0%) whereas, there were two OHSS (3.6%) in the coasting group, however, this differences was not significant. Thus, it was concluded that 0.5 mg daily use of cabergoline for 8 days, on the day hCG administration is a very effective ways to reduce moderate severe OHSS without scarificing pregnancy rate in patients at risk of developing OHSS.[12]

Alvarez et al[3] conducted a randomized, placebo controlled double blind clinical trial in oocyte donors at risk of OHSS and found that the incidence of moderate or severe OHSS was significantly reduced in the cabergoline treated group, without an adverse effect in ovarian function.[2,14]

In a study by Aflatoonian A et al on cabergoline *vs* coasting in prevention of severe OHSS cabergoline adminstration was as effective as coasting for prevention of early severe OHSS and concluded that this method is a pathophysiological approach, time saving and lead to higher pregnancy rate than coasting.[15]

In Cochrane review of two studies involving 230 women oral cabergoline 0.5 mg daily, with a matched placebo, a statistically significant reduction in OHSS was observed in the cabergoline treated group (OR 0.40, 95%, CI 0.20 to 0.77) with a number needed to treat (NTT) of seven. There was a statistically significant difference in the incidence of moderate OHSS, favoring cabergoline (OR 0.38, 95%, CI 0.19 to 0.78) but not in severe OHSS (OR 0.77, 95% CI 0.24 to 2.45) Thus, it was conducted that cabergoline appears to reduce to risk of OHSS in high risk women, especially for moderate OHSS. The use of cabergoline does not affect the pregnancy outcome (clinical pregnancy rate, miscarriage rate) in this review.

In the meta-analysis of randomized controlled trials by Valeria MS Leitao et al[16] all included studies used different comparaters 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 starting at hCG injection, 0.5 mg/d cabergoline for 3 weeks + 20 gm albumin at oocyte retrieval compared with 20 gm albumin at oocyte retrival;[3] 0.25 mg/d cabergoline for 8 days, starting at hCG injection + 500 ml HES (hydroxyl ethyl starch) at oocyte retrieval, compared with 500 ml HES at oocyte retrieval.[17] 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 initial pregnancy test; 0.5 mg/d cabergoline for 7 days, starting at oocyte retrieval, compared with 20 gm albumin at oocyte retrieval,[18] 0.5 mg/d cabergoline for 7 days starting at hCG injection, compared with coasting (i.e. ceasing gonadotropin and with holding hCG injection initial E_2 reaches < 3000 pg/ml); and 0.05 mg/d cabergoline for 12 days, starting at oocyte retrieval compared with 20 gm albumin at oocyte retrieval.

It was concluded in the meta-analysis that cabergoline reduces the incidence of OHSS when used by women who are at high risk for that complication while undergoing CO. Uncertaininity still exists regarding the impact of cabergoline on live births, congenital anomalies and miscarriage.

Shalt Out et al 2012 found that cabergoline reduces OHSS incidence in high risk patients without compromising the pregnancy outcomes.[17]

Tehraninijad et al concluded that cabergoline is better than human albumin for decreasing the incidence and severity of OHSS.[18]

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.[14,17,18]

CONCLUSION

A 0.5 mg daily use of dopamine agonist cabergoline, begining from hCG administration is associated with significant reduction in the occurrence of moderate to severe OHSS.[2]

Further, research is warranted comparing cabergoline with other established treatment. Cabergoline does not influence clinical pregnancy rate or miscarriage rate.[2,14,17,18]

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