

# Role of Cabergoline in High Risk for Ovarian Hyper Stimulation Syndrome (OHSS) Prophylaxis Undergoing IVF/ ICSI Treatment Cycles

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## ABSTRACT

**Background:** Ovarian hyper stimulation syndrome (OHSS) is defined as a complication related to stimulation of ovaries and is considered a life threatening condition of unknown etiology.

**Aim:** To see the effect of cabergoline (dopamine agonist) as preventive therapy in ovarian hyper stimulation syndrome (OHSS) during IVF/ICSI treatment cycles.

**Study design:** Prospective cohort study

**Study period:** 22 months period. From August 2015 to June 2017

**Methods:** Fifty females who were having risk factors of developing OHSS and were undergoing IVF/ICSI treatment cycle, these patients were given 0.5 mg of cabergoline (Dostinex) from the day of ovum pickup for total of eight day. Married couple whose spouses have not conceived after one year of unprotected sex, pcos, age less than 30 year, low BMI, No of eggs picked up for ICSI = 20 eggs or more. Ovarian size from 10 -15 cm± ascites. E2 level on day of ovum pick up >3000pg/ml smoking, obesity, diabetes mellitus, age more than 30 years. Estrogen more than 5000pg/ml. Data analysis: Statistical analysis was carried out using SPSS version 19.0, Student's *t* test was used to detect significance of cabergoline use in sub fertile females.

**Results:** 50 sub fertile women were included and assessed, there was significant lowering of OHSS with the use of cabergoline the dopamine agonist reduced the occurrence of the severe and moderate OHSS by 50%. But more significant reduction was seen in moderate OHSS, as fewer cases of severe OHSS was seen. No difference in live birth rate and ongoing pregnancy rate was observed in patients who were taking cabergoline.

No significant side effects of cabergoline have observed during study period.

**Conclusion:** Use of dopamine agonist cabergoline at doses (0.5 mg) to prevent OHSS in females at high risk is very effective in reducing chance of OHSS and in IVF/ICSI treatment cycles.

**Keywords:** OHSS, dopamine agonist, IVF, ICSI

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## INTRODUCTION

Ovarian hyper stimulation syndrome (OHSS) is defined as a complication related to stimulation of ovaries and is considered a life threatening condition of unknown etiology. Its incidence is from 1–14% of patients<sup>1</sup> of all IVF/ICSI cycles. OHSS is characterized by immense enlargement of ovaries, fluid accumulation in abdomen, thoracic filling with fluid, abnormal liver & renal functions, it sometimes need to cancel an IVF cycle, might need hospital admission which leads to emotional and economic disturbances in patients. But exact pathophysiology of this hyper stimulation is not clearly known<sup>2,3,4,5,6</sup>, early form of OHSS seen after HCG injection which is because of exogenous HCG and ovarian response to it, and is mostly seen within 3–7 days HCG injection, late form caused by endogenous HCG and seen within 10–17 days later<sup>7</sup>. Not only HCG, but vascular endothelial growth factor (VEGF) which is a vasoactive substance also takes part in the growth of Ovarian hyper stimulation syndrome OHSS<sup>8</sup>. Different methods have seen to avoid OHSS, i.e., cancelled IVF cycle, coasting<sup>9</sup>. intravenous albumin administration<sup>10</sup>, In GnRh antagonist protocol cycle, GnRh agonist is used to trigger oocyte<sup>11</sup>.

Using natural-cycle for ICSI or to mature oocyte<sup>12</sup>. In spite of using urinary HCG, Use recombinant HCG<sup>13</sup>. Use metformin for OHSS prevention<sup>14</sup>. Freeze all embryos and transferred in next cycles<sup>15</sup>. However none of them was successful in preventing this syndrome. Dopamine agonist is used to decrease the severity of OHSS as a new strategy<sup>16</sup>. A lot of trials have been done in recent years to see the effectiveness of a dopamine agonist to lower the recurrence and severity of Ovarian hyper stimulation syndrome OHSS<sup>17</sup>. The objective of this study is to see the role of dopamine agonist to decrease the recurrence and severity of Ovarian hyper stimulation syndrome OHSS in patients who are at high-risk for ovarian hyper stimulation & undergoing IVF/ICSI treatments.

## MATERIALS AND METHODS

Fifty females with sub fertility who were taking ICSI treatment at IVF/ICSI center were selected. All were having risk factors for developing ovarian hyper stimulation syndrome (OHSS). Study period was included between August 2015 and June 2017. The risk factors were (a) level of E2 more than 3500 pg/ml on the HCG trigger day, ovaries having follicles more than 20 and follicular size of

Received on 11-10-2018

Accepted on 10-12-2018

greater than 12mm. Patients having E2 levels 5000 pg/ml were the exclusion criteria of study. A written informed consent was given by patients on a consent form. Pituitary down regulation was done with the help of 0.1 mg triptorelin SC , for controlled stimulation a stable dose of 150–225 IU of HMG (Menogon 75 IU, IM injections) were used for five days, the dose was later adjusted with the ovarian response. Follow up done by using TVS and serum estrogen levels on alternate day. When size of at least three lead follicles up to 17 to18 mm reached, oocyte triggered with help of HCG 5000 IU in a single dose, which is our center strategy. On same day we started 0.5 mg/day cabergoline for next eight days. Ovum pick up was done 34–36 h after HCG injection. Two embryos were transferred 72 hours later under ultrasound guidance. The luteal support was given with help of cyclogest passeries (400 mg) per vagina two times a day till the time of beta HCG test positive for pregnancy. Heamo-concentration, ascites, presence of free fluid in the pouch of Douglas, increased volume in ovaries were seen the day when ET done & after 1 week. The primary outcome measure was according to Golan’s classification as a decrease in the OHSS frequency<sup>17</sup> & mild, moderate to severe forms of OHSS was considered as secondary outcome. OHSS was categorized as early if was happened in less than 7 days and remained for up to 10 days. OHSS having duration of (10-17 days) was categorized as late, quantity of mature oocytes retrieved, need to hospitalize the patient because of disease severity, how many oocyte fertilized, clinical pregnancy rate (which is positive beta-HCG test after 14 days of administration indicative of positive fetal heart beat), with alive birth frequency. Statistical analysis was performed using SPSS Version 19. To evaluate the significant statistical differences in variables, Students-t test was done. Significance level was taken as p-value of 0.05. Approval was taken from institutional ethical committee before performing the study. Written as well as informed consent from the subjects will be taken before start of the study. The subjects who refuse to give consent were excluded from the study.

**RESULT**

Fifty sub fertile females were included and assessed, In cabergoline was used .It was seen that in cabergoline group the incidence of OHSS was only 8.30% with relative ratio of 0.5% and 95% confidence interval. 50 sub fertile women were included and assessed. No significant side effects of cabergoline (nausea, vomiting, light headedness, hypotension or blurring of vision) had observed during study period.

Table 1: Demographic data of females taking cabergoline

|                          |       |
|--------------------------|-------|
| 1.Age (years)            | 31.07 |
| 2.BMI(kg/m)              | 23.90 |
| 3.E2 on day of HCG       | 5500  |
| 3.Antral follicle count  | 24.00 |
| 4.Cause of sub fertility |       |
| Male                     | 04%   |
| Female                   | 14%   |
| Unexplained              | 17%   |

There was significant lowering of OHSS with the use of cabergoline (dopamine agonist) by 50% in reducing the occurrence of the moderate and severe form of OHSS. But more significant reduction seen in moderate OHSS, as fewer cases of severe OHSS was seen. No differences were observed in the frequency of continued pregnancies and live births rate in patients who were taking cabergoline.

Table 2: Outcomes of Cabergoline use in females

| OHSS        | Cabergoline group |
|-------------|-------------------|
| Incidence % | 3(8,30)           |
| Severe %    | 0                 |
| Moderate%   | 3(8,30)           |
| Mild %      | 0                 |

**DISCUSSION**

Cabergoline lowers the occurrence of OHSS in treatment cycles of IVF and ICSI. Assuming high risk patient for an ovarian hyper stimulation syndrome OHSS, we started using cabergoline, control rate was of 25%. This tells us that to prevent one patient of OHSS we must give nine patients dopamine agonist. Also, the incidence is rare in OHSS severe form. We need to have larger trials to show that severe form of OHSS is rare or more. But with our data we conclude especially that risk of OHSS forms (moderate & severe) was decreased with the use of cabergoline in high risk women. Cabergoline use did not had any effect on the pregnancy outcome nor there do any risk of adverse events. There were no significant difference seen in the frequency of continued pregnancies, live births & miscarriage rate<sup>18</sup>. One study was<sup>19</sup>, biased that gave exaggerated results of cabergoline use. But in most of studies the results were same in all trials. Sensitivity was checked randomly through meta-analysis. Efficiency of dopamine agonist as effective prophylaxis for OHSS was also proved non-randomly. In one trial improvement in twenty patients who were admitted in hospital at risk of OHSS ,It was seen recently, dopamine agonists cabergoline have been seen very useful and successful for the treatment of OHSS in patients at risk and have reduced the severity of OHSS. They also reverse increased vascular permeability in patient with hyper stimulation by inhibiting phosphorylation of VEGFR-2. Another nonrandomized trial, Cabergoline was used in twenty seven patients having OHSS & in twenty (74.1%) patients very satisfactory results seen, patients’ recovery from clinical symptoms of OHSS was quick and complete<sup>20</sup>. Cabergoline has various ill effects as a drug and was a point of inquiry for patients in causing the endometrial vascularization, implantation of embryo, and abortion rates. No consistent and secure results were found in newly born while used for long period of time. No relation seen between dopamine agonist and endometrial angiogenesis, ongoing pregnancy rates and miscarriage rates in all these studies. In two other RCT pregnancies in women were followed till the end and found no effect on the live birth rate seen<sup>17</sup>. For prolonged cabergoline effects, there were also three non-randomized trials, in first trial, 205 females taking cabergoline resulted in 226 pregnancies, and in 204 pregnancies follow up was done. Out of total twenty four miscarriages, three were induced due to malformed babies. So abortion rate was not increased significantly, and there

was no relation with birth weights, sex ratio or any rise in congenital malformations<sup>21</sup>. Also, in the treatment of hyperprolactinaemia with the use of cabergoline, 61 pregnant females gave data in second trial. Results suggested 12 early terminations (5 induced, one hydatidiform mole, & 6 unplanned abortions), 38 were live births. One pregnancy terminated due to malformed baby at 12 weeks gestation, trisomy 18 was also present as one of incidence. The rate of unplanned, miscarriages and deformities were same as in the general population<sup>22</sup>. Another was retrospective pilot study to see effectiveness of cabergoline as OHSS prophylaxis in 35 at risk of OHSS females and were given cabergoline in controls at more risk and not taking cabergoline. Similar results were found in both the groups (38.6% and 41.4%) for implantation, no changes in rate of live births (40% in two groups). Deformities were not seen in any of the new born<sup>20</sup>, because the sample size was too small so in females as well as in babies, there is still consistent results lacking prolonged characteristics of dopamine agonist. In recent days dopamine agonist's usage such as cabergoline and pergolide has resulted in valvular heart defects in parkinsonian patients using them for long time in heavy doses<sup>23</sup>. In many trials in prolactinoma dopamine agonist doses are 10-fold lower than those used in Parkinson's disease but no valvular heart disease observed<sup>24</sup>. However, prolactinomic patients in RCT, with the usage of cabergoline there were no obvious bad effects with prolong usage. No effect were seen on heart valve regurgitation with cabergoline treatment in the present study, duration of cabergoline treatment.

At last, nothing is known about the true causes of OHSS. So, prophylactic treatment in OHSS is not specific. It is concluded that there is a need for further studies to predict the effectiveness of cabergoline in lowering the risk of OHSS.

## CONCLUSION

It was concluded that use of dopamine agonist, cabergoline as prophylactic in treating OHSS significantly decreased the occurrence of OHSS, but no effects were observed in lowering the severity of OHSS, with safe outcomes of pregnancy

**Grant Support & Financial Disclosures:** None

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