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Original Research Article

Efficacy of cabergoline in the prevention of severe ovarian hyperstimulation syndrome in high-risk women undergoing assisted reproductive technology treatment

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ABSTRACT

Background: Ovarian hyperstimulation syndrome (OHSS) is a severe and potentially life-threatening complication of controlled ovarian stimulation (COH). Cabergoline has been tried as a preventive measure for OHSS in high-risk women undergoing assisted reproductive technology (ART) treatment. Our study was done to assess the effectiveness of cabergoline in preventing severe OHSS in high-risk women undergoing ART treatment.
Methods: This is a prospective interventional study done among patients undergoing ART with serum estradiol levels >4000 pg/ml on the day of hCG administration were included in the study. Women undergoing ART with serum estradiol levels >4000 pg/ml on the day of hCG administration, were assigned into two groups using random number allocation. Women in treatment group received cabergoline 0.5 mg daily for 8 days from the day of hCG administration and control group did not receive Cabergoline therapy. The patients in both groups were followed up to study the incidence and severity of OHSS in that treatment cycle
Results: The incidence of severe OHSS was two in each group with clinical and ultrasound evidence of ascites. Embryo transfer was cancelled in one patient in each group in view of severe OHSS with tense ascites. One patient in treatment group had severe OHSS that needed peritoneal fluid tapping with fresh frozen plasma administration. Life threatening complications were not encountered in any of the patients with high risk for OHSS included in the study.
Conclusions: Cabergoline did not prevent the incidence of severe OHSS in patients at high risk for OHSS in our study. Large randomized trials would be needed to confirm the findings of our study.

Keywords: Cabergoline, OHSS, ART

INTRODUCTION

Ovarian hyperstimulation syndrome (OHSS) is an iatrogenic, severe and potentially life-threatening complication of COH. Its incidence is second to higher order multiple births in the list of adverse outcomes in Assisted reproductive technologies (ART) cycles.[1] OHSS consists of ovarian enlargement accompanied by overproduction of ovarian hormones and vasoactive substances which increases vascular permeability causing signs, symptoms and complications of OHSS. Severe OHSS is characterized by severe abdominal distension, dyspnea, tachypnea, lower abdominal pain, hypotension, hemo-concentration, oliguria, hydrothorax, thromboembolic phenomenon, hyponatremia and hyperkalemia. Therefore, prevention of severe OHSS forms an important aspect of ART cycles.[1] Severity of OHSS was classified according to classification by Rizk

and Aboulghar.[2] There is no specific cure for OHSS other than providing supportive measures.

Many preventive strategies have been tried to prevent severe OHSS. It includes cycle cancellation, coasting, intravenous albumin administration around the time of oocyte retrieval, GnRH agonist trigger in antagonist cycle, *in vitro* maturation and natural cycle IVF.[3-9] Cabergoline, a dopamine agonist has been tried as a preventive measure for OHSS in high-risk women undergoing ART treatment.[10-14]

Vascular endothelial growth factor (VEGF) also known as vascular permeability factor is one of the factors most likely involved in the pathophysiology of OHSS. Dopamine prevents a VEGF effect on vascular system, i.e., reducing VEGF receptor 2 expression/phosphorylation by a D2 receptor mechanism.[15] Hence dopamine, specifically D2 dopamine agonists may be used in prevention as well as treatment of OHSS, specifically severe OHSS. Cabergoline (Cb2) is an ergot derivative with D2 dopamine receptor agonistic action.[16] Its safety is established during pregnancy.[17] Fertilization, implantation and pregnancy rates were not affected by cabergoline treatment[18] and the frequency of miscarriages and major congenital malformations were similar to that of general population.[19] This study aimed to assess the effectiveness of dopamine agonist cabergoline in preventing severe OHSS in high-risk women undergoing ART treatment.

METHODS

This was a prospective interventional study done over a period of one year among patients undergoing ART. The study was done after obtaining Institute ethics committee approval. Patients undergoing ART with serum estradiol levels >4000 pg/ml on the day of hCG administration, who consented to participate in the study were included in the study. A total of 50 patients were enrolled in the study. These women were assigned into two groups: Women in group A (Interventional arm) received cabergoline 0.5 mg daily from the day of hCG administration for 8 days. Women in group B (Control arm) did not receive Cabergoline.

All the patients for ART were treated with long GnRH agonists protocol. These women were followed up with hemogobin (Hb), packed cell volume (PCV) and ultrasound evidence of ascitic fluid on the day of hCG administration, the day of ovum-pick up (OPU) and the day of embryo transfer (ET). Evidence of free fluid in pouch of Douglas was observed by transvaginal scan and in the presence of fluid in pouch of Douglas, transabdominal scan was done to observe for the presence of free fluid in hepatorenal pouch.

All patients were followed on outpatient basis. These women were informed about the symptoms of severe OHSS and were asked to inform their hemoglobin and PCV values on day 5 after Embryo transfer through telephonic conversation and to report if any symptoms of severe OHSS like nausea, vomiting, diarrhea, abdominal pain, abdominal distension, shortness of breath or decreased urine output developed. Serum βhCG value was checked on day 14 after embryo transfer and value more than 50 mIU/ml was considered positive. The outcome studied was the incidence of severe OHSS. Severe OHSS was diagnosed when clinical signs of ascites, hydrothorax, shortness of breath, hemo-concentration, hypercoagulability, or any complications of OHSS such as renal failure, thromboembolism or acute respiratory distress syndrome were present.

Statistical analysis

The Statistical software SPSS 15.0 was used for the analysis of the data and Microsoft word and excel have been used to generate graphs, tables etc**.** Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups (Inter group analysis) on metric parameters. Chi-square/ Fisher exact test has been used to find the significance of study parameters on categorical scale between two or more groups. P≤0.05 was taken as statistically significant

RESULTS

The age of patients in cabergoline group (cases group) and control group was 30.1±4.5 and 29.8±5.5 years respectively. The distribution of primary and secondary infertility was same in both the studied groups. Women with primary and secondary infertility were similar in both groups (68% and 36% respectively). The duration of married life in patients in cabergoline and control group was 8.2±4.8 and 7.9±5 years respectively. Mean married life in years is statistically similar in two groups with p=0.792. The duration of trying time for pregnancy in patients in cabergoline group and control group was 5.5±3.7 and 5±3.5 years respectively. Mean trying time is statistically similar in two groups with p=0.621. The incidence of PCO was statistically similar in both groups with incidence of PCO being 24% in and 12% in control group (p=0.299). The 8% and 96% underwent their first attempt of ICSI in cabergoline group and control group respectively (p=0.189). The average dose of gonadotropin received by women in cabergoline group and control group was 257±91.4 and 263±106.8 IU/day respectively. Mean dose is statistically similar in two groups with p=0.832. The duration of gonadotropins required cabergoline group and control group was 9.9±1.5 and 10.8±1.6 days respectively. Mean duration in days is significantly less in cabergoline group with p=0.043.* While comparing the hormonal profiles, women with serum estradiol levels at 4000-4300 pg/ml and >4300 pg/ml were comparable between the two groups (Table 1).

Table 1: Comparison of hormonal parameters in both groups studied, (n=25).

Hormonal parameters	Cabergoline group, n (%)	Control group, n (%)	P value
Serum estradiol (pg/ml)			
4000-4300	11 (44)	12 (48)	0.777
>4300	14 (56)	13 (52)	
Serum LH (miu/ml)			
<1.0	1 (4)	6 (24)	0.243
1.0-2.0	12 (48)	11 (44)	
2.0-3.0	8 (32)	5 (20)	
>3.0	4 (16)	3 (12)	
Serum progesterone (ng/ml)			
<1.0	16 (64)	18 (72)	0.630
1.0-2.0	8 (32)	5 (20)	
>2.0	1 (4)	2 (8)	

The embryological parameters such as the number of follicles >12 mm, number of oocytes, number of MII oocytes, number of embryos and the number of embryos transferred were comparable between 2 groups (Table 2).

Table 2: Comparison of embryological parameters in both groups studied, (n=25).

Embryological parameters	Cabergoline group, n (%)	Control group, n (%)	P value
No. of follicles >12 mm	20±1.8	22.9±1.9	0.267
Oocytes no.	22.6±2.3	25.1±2.4	0.456
Mii oocytes no.	13.5±1.4	17±1.9	0.139
No. of embryos	8.9±1.1	12.2±1.4	0.073+
No. of embryos transferred	2.9±0.1	3±0.1	0.321

Hemoglobin Level was statistically similar in both groups on the day of HCG administration, on ovum -pick up day, on the day of embryo transfer and on day 5 after embryo transfer (Table 3).

Table 3: Comparative evaluation of hemoglobin in both groups studied, (n=25).

Hemoglobin (g/dl)	Cabergoline group, n (%)	Control group, n (%)	P value
On day of HCG administration	11.7±1	11.5±1	0.58
On ovum-pick up (OPU) day	11.6±1	11.5±1.1	0.878
On embryo Transfer (ET) day	11.4±1	11.5±1.1	0.752
On 5th day after embryo transfer	11.3±1.3	11.2±1.2	0.951

PCV values was statistically similar on the day of HCG administration, on ovum –pick up day, on the day of embryo transfer and on day 5 after embryo transfer in both the groups studied (Table 4).

Table 4: Comparative evaluation of PCV in both groups studied, (n=25).

PCV %	Cabergoline group, n (%)	Control group, n (%)	P value
On day of HCG administration	36.7±3.5	35.7±3.5	0.289
On ovum-pick up (OPU) day	36.5±3.2	36.1±3.3	0.667
On embryo transfer (ET) day	36.4±3.1	35.6±3.6	0.424
On 5th day after embryo transfer	35±3.5	33.9±6	0.403

Presence of free fluid was statistically similar on the day of HCG administration, on ovum pick up day and on the day of embryo transfer in both the groups studied (Table 5).

Table 5: Comparative evaluation of free fluid in both groups studied, (n=25).

Free fluid (Yes)	Cabergoline group, n (%)	Control group, n (%)	P value
On HCG-day	4 (16)	7 (28)	0.496
On ovum-pick up (OPU) day	6 (24)	11 (44)	0.232
On embryo transfer day	6 (24%)	13 (5)	0.079

There were four patients with severe OHSS, two each in both groups studied. Hence the incidence of severe OHSS was similar in both groups. All the four patients who developed severe OHSS had early onset OHSS, occurring in the first week after ovum pick up (Table 6).

Table 6: Comparison of incidence of severe OHSS in both groups studied, (n=25).

Severe OHSS	Cabergoline group, n (%)	Control group, n (%)	P value
No	23 (92)	23 (92)	1.000
Yes	2 (8)	2 (8)	

DISCUSSION

In our study, the age group of patients, the incidence of PCO, the duration of married life, the type of infertility (Primary/secondary) were all comparable in both groups.

In our study, we have considered patients with serum E2 levels>4000 pg/ml on the day of hCG as high-risk group. In other studies, inclusion criteria were based on serum estradiol values on the day of hCG or follicular number or both. In study by Alvarez et al among 82 oocyte donors, risk of developing OHSS was defined by the development of 20–30 follicles larger than 12 mm in diameter and retrieval of more than 20 oocytes. Shaltout et al had considered 200 women undergoing ICSI with serum E2 >3500 pg/ml on hCG day plus 20 follicles with 10 mm baseline at high risk for OHSS.[2]

In our study, we had given oral cabergoline 0.5 mg day once daily at bed time from the day of hCG administration for eight days. There is clinical heterogeneity between various trials in the dose of cabergoline either 0.5 mg 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 (ii) one 0.5 mg tablet of cabergoline daily for 8 days from the day of hCG injection (Alvarez et al) (iii) 0.5 mg, one tablet on two successive days, repeated 1 week later, starting from day of hCG injection (Salah Edeen et al) (iv) Cabergoline 0.25 mg daily for 8 days from the day of hCG injection (Shaltout et al), (v) 1 mg every other day for 8 days from the day of ovum pick up by Hosseini et al.[13,16,20-22] In our study, we had started cabergoline a few hours before hCG injection rather than on ovum pick up day because logically hCG injection increases VEGF expression and hence giving a Dopamine agonist on the day of hCG would be more meaningful than on ovum pickup day.

The values of hemoglobin and PCV were comparable in both groups. Severe OHSS is evidenced by marked hemo-concentration with PCV >45%. Surprisingly, our group of patients never had such high biochemical values. The probable explanation being that these high-risk patients were closely monitored, and hospitalization and treatment were begun early, without patient proceeding to critical stage. Such high values are possible in late cases of OHSS (due to endogenous hCG rise) and in case of patients with late referral. The incidence of severe OHSS was two in each group with clinical and ultrasound evidence of ascites. Embryo transfer was cancelled in one patient in each group in view of severe OHSS with tense ascites. One patient in cabergoline group had severe OHSS that needed peritoneal fluid tapping with fresh frozen plasma administration. Life threatening complications of OHSS like hydrothorax, renal failure, thromboembolism or acute respiratory distress syndrome were not encountered in our study. Thus, in our study we found no difference in incidence of severe OHSS when cabergoline is used compared with no treatment.

Cochrane review in 2012 analyzed the effectiveness and safety of cabergoline in preventing OHSS in high-risk women undergoing ART treatment. According to this review, there is no evidence that the use of cabergoline reduces the risk of severe OHSS. The number needed to treat (NNT) to avoid one case of moderate OHSS was eight (95% CI 4 to 25); to avoid one case of severe OHSS the NNT was 100. This means for every 100 people at risk of OHSS treated with cabergoline, 14 cases of OHSS, (one of severe OHSS and 13 of moderate OHSS) would be avoided.[12] The results of our study similar to that of Cochrane review with no evidence that cabergoline reduces incidence of severe OHSS as preventive measure.

Limitations

Our study results may possibly be due to the small sample size and low incidence of severe OHSS in the study population. Trials with larger samples would be needed to detect a statistically significant difference. Hence routine use of it may be considered with caution until trials showing definitive protective role are published.

CONCLUSION

It may be concluded from our study, that Cabergoline did not reduce the incidence of severe OHSS in patients with high risk for OHSS undergoing IVF, compared to those patients who did not receive cabergoline. Routine use of Cabergoline as a preventive drug for severe OHSS cannot be advocated with the present data and evidence. Large randomized trials would be needed to confirm the findings of our study.

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