Cabergoline as a preventive measure against ovarian hyper-stimulation syndrome in assistive reproductive programs

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Abstract. Ovarian hyperstimulation syndrome is one of the complication appearing not immediately but in early phases of pregnancy, in the luteal phase. The aim of this study was to investigate the effectiveness of cabergoline in the prevention of severe OHSS, assess its impact on the process of embryo implantation.

It was observed 192 women receiving IVF treatment against infertility and studied the effectiveness of cabergoline in women with early and late forms of ovarian hyperstimulation syndrome.

We determined that the women prescribed cabergoline had fewer reproductive losses against those of the control group and our studies showed that use of cabergoline since the introduction of ovulation trigger decreases early and late types of severe OHSS.

Introduction. One of the most dangerous complications while applying assistive reproductive technologies (ART) during infertility treatment is ovarian hyperstimulation syndrome (OHSS).

Taking into account that ART has become more widespread recently, the risk of OHSS has increased, as well. Generally, major symptoms of this complication appear not immediately but in early phases of pregnancy, in the luteal phase.

OHSS is characterized by enlarged ovaries, raised oestradiol to a critical level in blood, redistribution of fluid to a part known as “third space” which in turn may cause development of haemoconcentration, faulty perfusion, and thromboembolism [2,5].

Severe cases constitute 9-15% of all OHSS cases. The cases ending in death are rare. According to info by World Health Organization (WHO), it is 1 in every 50,000 cases [4]. Most of the time what cases them are renal-hepatic failure, cerebral infarction, thromboembolism, respiratory-distress-syndrome. Besides hazards it poses to women, OHSS also creates unfavorable condition for development of implanted embryo [6]. The end-result is frequency of early reproductive losses, most notably in pregnant women with mid and high clinical conditions [2].

There are numerous methods to treat and prevent OHSS but no effective means have been produced yet against OHSS that would not negatively affect frequency of pregnancy, and as well as not cause increase in early reproductive losses. Recently, there have been news regarding use of selective dopamine receptor agonists on D2 receptors (one of which is cabergoline) within treatment and prevention of OHSS [7].

Preventive effect of cabergoline to the risk of development and progression of OHSS is associated with the ability of its specific receptor type 2 (VEGF R2) to block the interaction of vascular endothelial growth factor (VEGF) located on the endothelium, strongly formed by OHSS [1]. The result of the blockade of VEGF effects is reduction in vascular permeability, which helps eliminate the trigger level in the pathogenesis of clinical manifestations of OHSS [1].

It is known that VEGF and VEGF R2 exist in ovarian tissue, namely in granulosa cells and corpus luteum and that VEGF is responsible for the increased vascular permeability. The mechanism of the mentioned process, binding of VEGF and receptor type 2 (VEGF R2), plays a key role in the change in vascular permeability.

Gonadotropins used in IVF stimulation protocols, increase the effect of VEGF R2, which reaches its maximum after the delivery of human chorionic gonadotropin (hCG). In this way, VEGF R2 will be directly correlated with the level of vascular permeability [3].

It was also found that increased delivery of VEGF casuses reduced production of dopamine. Dopamine agonists have the ability to phosphorylate the receptor VEGF R2 and convert VEGF R2
into a form that is not capable of binding with growth factor, a prevention against increase in vascular permeability and the development of OHSS [3, 7]

It noteworthy to state that cabergoline is quite safe in the treatment of patients with prolactinomas and this makes its introduction easier into clinical practice for the prevention of OHSS. However there are certain questions that remain open: what are the criteria for the prescription of cabergoline, in what dosages it should be administered, in what period of controlled ovarian simulation it should be administered, how safe it is in the process of implantation of transferred embryos, how it affects pregnancy rate, and whether there is connection between use of cabergoline and reproductive losses. [4, 8]

Considering aforementioned points, we have set our goal in this paper: to study the effectiveness of cabergoline in the prevention of severe OHSS, assess its impact on the process of embryo implantation, pregnancy rate and the incidence of early reproductive losses in Azerbaijani population.

Materials and methods: between years 2009 and 2013 192 women receiving IVF treatment against infertility were examined at Central Clinic Hospital, Baku. Target group who received cabergoline were 98 people while the control group were 94. In the preparatory phase to IVF, all patients went through standard examinations-which included ultrasonography, hormonal profile on 2-3 days of the menstrual cycle (FSH, LH, TSH, free T4, T3, prolactin, estradiol, testosterone, progesterone, hysterosalpingography (HSG ). There has also been examining of the infection status, and evaluation karyotyping. Women with polycystic ovary syndrome (PCOS) were required to undergo glucose load test (100 mg), to determine glycohemoglobin and insulin levels. Controlled ovarian hyperstimulation was performed by standard antagonist protocols, used drugs - Fostimon, Puregon, Bravel, Merional, and Menogon. For ovulation pregnyl, choriomon, and Dekapeptil agonists.

Statistical processing: Obtained results were processed using variations statistics method through the computer software “EpiInfo 7”. While analyzing relative risk level confidence interval of 95% was calculated. While comparing differences, statistical significance for values of p<0.05 was calculated.

Results. All patient groups studied were from 20 to 38 years old, the average age was 29. All patients came to the clinic complaining of infertility, and it was the primary reason for all of them. As shown in figure 1, menstrual dysfunction was observed in 89 patients, and the type oligomenorrhea in 47 (53%), amenorrhea in 22 (25%), hyperpolymenorrhea- 20 (22%). We did not observe dysfunctional uterine bleeding in our patients. Anovulation was diagnosed in 49 patients.
Structure of gynecological and somatic diseases was examined. Of gynecological diseases cervicitis and vaginitis were dominant. With regard to somatic diseases the leading diseases were of the gastrointestinal tract.

When any abnormalities prior to the IVF program are identified there is a compulsory treatment of infections, sexually transmitted diseases and TORCH panel infections, as well as correction of hormonal and metabolic disorders following more research and expert advice.

During hyperprolactinemia bromocriptine drugs or dopamine receptor agonists (Dostinex) are prescribed after conducting magnetic resonance imaging (MRI) of the pituitary, and consultation with neurosurgeon and endocrinologist.

During hyperfunction of the adrenal cortex glucocorticoids drugs were administered.

Thyroid dysfunction was eliminated with appropriate medication after ultrasonography of the thyroid gland and consultation with an endocrinologist. After a series of tests and examinations on patients with PCOS who were overweight, had hirsutism, hyperinsulinemia and impaired glucose tolerance, we were able to correct metabolic and endocrine disorders through food diet and drugs that lower body weight, hyperinsulinemia and hyperandrogenism.

Patients received medication of 1000 mg dose "Metformin" or "Siafor" per day during 2-3 cycles. The criteria for the adequacy of the treatment is the reduction in body weight, normalized glucose tolerance test, normalization of glycohemoglobin level and hormonal parameters in blood.

We have also examined the main causes of infertility in our study groups.

Table 1.
Etiological reasons of infertility in target and control groups.

<table>
<thead>
<tr>
<th>Etiological factors</th>
<th>Control group n=94</th>
<th>Target group n=98</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCOS</td>
<td>44</td>
<td>48</td>
</tr>
<tr>
<td>Tubal factor</td>
<td>19</td>
<td>12</td>
</tr>
<tr>
<td>Anovulatory cycle</td>
<td>22</td>
<td>27</td>
</tr>
<tr>
<td>Idiopathic infertility</td>
<td>9</td>
<td>11</td>
</tr>
</tbody>
</table>

It should be noted that all the women were reported to be with normal uterus, a normal karyotype by ultrasonography. On the Hysterosalpingography (HSG) test 12 women were reported to have one or two-sided hydrosalpinx, to whom during the preparatory phase laparoscopic tubectomy and / or tubal ligation were carried out.
All the husbands of studied patients had normal semen and normal karyotype.

All the patients in target and control groups underwent controlled superovulation simulation due to antagonist protocol.

50 patients in the control group of 94, and 54 patients in the target group of 98 - superovulation was carried out with the use of drugs containing human menopausal gonadotropin HMG (menogen, Merional, Menopur) on their 2nd-3rd day of menstruation, for other patients stimulation was started with the use of FSH -containing drugs (Puregon, Fostimon, Gonal-F, Bravel). When the follicles reached diameter of 13-14 mm by about 6-8 days of the menstrual cycle, ie, the day of the treatment FSH antagonists were combined with HMG - containing drugs. As antagonists used daily injections Tsetrotida 0.25 mg or 0.25 mg Orgalutran.

We used hCG and / or agonists (Decapeptyl) as ovulation triggers. The criterion for selection was the number of stimulated follicles and estradiol levels in the blood.

If the number of stimulated follicles was less than 20, and estradiol levels were less than 5000 mol, the patient was administered 10 000 mg hCG. This subgroup, we named $a$.

If the number of stimulated follicles were more than 20, and estradiol levels were less than 5000 mol, two injections of Decapeptyl and 5000 IU hCG were designated for this subgroup we called $b$.

If the number of stimulated follicles were more than 20, and estradiol levels were less than 5000 mol, only two injections of Decapeptyl were designated for this subgroup we called $v$.

For these last two groups, on the day of the appointment of the trigger ovulation patients have begun taking Cabergoline 0.25 mg / day or 0.5 mg / day orally for 8 days. Dose of cabergoline was selected depending on the body-mass-index (BMI) of the patient.

When BMI was less than 25, 0.25mg/day Dostinex was administered while 0.50 mg/day Dostinex was administered for those over BMI of 25.

After embryo transfer all patients were administered progesterone (Crynon gel 8% or Utrogestan 200 mg) and continued to receive till pregnancy was confirmed or denied. If pregnancy was confirmed progesterone was administered till the 14th week of pregnancy.

After the introduction of the ovulation trigger, tracking the signs of OHSS we monitored the overall status of patients till the confirmation / denial of clinical pregnancy by ultrasound. All cases of OHSS occurring during the first days after the puncture of oocytes were regarded as early OHSS. Cases of all syndromes occurring 9 days after the puncture of oocytes were regarded as late OHSS. Note that at the time of the study, we only considered the cases of moderate and severe OHSS degree classification.

The effectiveness of IVF in the compared groups was assessed by the rate of pregnancy in the stimulated cycle (table 2). Patients with confirmed clinical pregnancy were further tracked in the I trimester, recording the incidence of early reproductive losses (miscarriages and developing pregnancy).

### Table 2.

<table>
<thead>
<tr>
<th>Analyzed indicators</th>
<th>Control group n=94</th>
<th>Target group n=98</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>subgroup a=30</td>
<td>subgroup b=30</td>
</tr>
<tr>
<td>Use of cabergoline</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Early OHSS (absolute numbers and %)</td>
<td>0 (4 (13.3%) )</td>
<td>10 (26.6%)</td>
</tr>
<tr>
<td>Late OHSS (absolute numbers and %)</td>
<td>0 (2 (6.6%) )</td>
<td>13 (10.0%)</td>
</tr>
<tr>
<td></td>
<td>subgroup a=30</td>
<td>subgroup b=30</td>
</tr>
<tr>
<td>Use of cabergoline</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Early OHSS (absolute numbers and %)</td>
<td>2 (6.6%)</td>
<td>3 (10.0%)</td>
</tr>
<tr>
<td>Late OHSS (absolute numbers and %)</td>
<td>5 (16.6%)</td>
<td>5 (16.6%)</td>
</tr>
</tbody>
</table>
As seen from the table, early and late OHSS cases appear less in target group who used cabergoline than the control group.

- B group (early OHSS) RR =0.3 (95% CI 0.09:0.9), p<0.05
- B group (late OHSS) RR=0.3 (95% CI 0.13: 0.9) p<0.05
- V group (early OHSS) RR=0.2 (95% CI 0.06:0.7) p<0.05
- V group (late OHSS) RR=0.4 (95% CI 0.17:0.9) p<0.05

We must also emphasize that cabergoline is relatively more effective means to prevent early OHSS than late OHSS.

As shown on the table 3, target group has much more pregnancy rate than control group. B group RR=0.6 (95% CI 0.4:0.9), p<0.05; V group RR=0.4 (95% CI 0.2:0.7), p<0.05.

**Table 3.**

Pregnancy rate in IVF patients compared groups based on factor use or non-use of cabergoline.

<table>
<thead>
<tr>
<th>Analyzed indicators</th>
<th>Control group n=94</th>
<th>Target group n=98</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>a=30</td>
<td>b=30</td>
</tr>
<tr>
<td>Use of Cabergoline</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Pregnancy rate (absolute numbers and %)</td>
<td>10 (33,3%)</td>
<td>6 (6%)</td>
</tr>
</tbody>
</table>

It should also be noted that use of cabergoline not only decreases the frequency of OHSS cases but also prevents further development of complications of OHSS. According to our results among women with OHSS, those treated with cabergoline had fewer cases with severe manifestations of OHSS than those patients developing OHSS- who did not use the drug.

Our studies have also shown that the use of cabergoline does not impair the ability to get embryo implantation and does not increase the relative risk of reproductive losses in the first trimester of pregnancy.

As seen from the table 4, target group that were administered cabergoline had fewer reproductive losses against those of the control group: RR=0.5 (95% CI 0.2:0.9) p<0.05.

**Table 4.**

Reproductive losses in the administration of cabergoline in studied groups.

<table>
<thead>
<tr>
<th>Analyzed indicators</th>
<th>Pregnant women who were NOT treated with cabergoline n = 94</th>
<th>Pregnant women who were treated with cabergoline n = 98</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy loss (absolute numbers and %)</td>
<td>24 (25.5%)</td>
<td>13 (13.2%)</td>
</tr>
</tbody>
</table>

Thus, our studies showed that use of cabergoline since the introduction of ovulation trigger decreases early and late types of severe OHSS, as well as not affect implantation capability of embryo nor increase incidence of early reproductive losses.
References


