Combined use of Letrozole, Cabergoline and GnRH antagonist Eliminates Ovarian Hyperstimulation Syndrome (OHSS) in Polycystic Ovarian Syndrome (PCOS)

Original Article

Yasuho Yanagihara[1,2], Atsushi Tanaka[1,2], Motoi Nagayoshi[1], Izumi Tanaka.[1], Motoharu Ohno[3] and Atsuo Itakura[2]

[1]Saint Mother Clinic, Department of Obstetrics and Gynecology, Kitakyushu, Japan.

[2]Juntendo University School of Medicine, Department of Obstetrics and Gynecology, Bunkyo-ku, Japan.

[3]Juntendo University Urayasu Hospital, Urayasu, Japan.

ABSTRACT

Aim: To determine if the properly timed, combined used of Letrozole, Cabergoline and GnRH antagonist eliminate the occurrence of ovarian hyper stimulation syndrome (OHSS) in polycystic ovarian syndrome (PCOS)?

Study Design: We compared the severity of OHSS after using a new treatment with the severity of OHSS in a group of PCOS patients who received the GnRH antagonist-GnRH agonist- based controlled ovarian stimulation (COS) in retrospective cohort study between August 2019 and December 2021.

Materials and Methods: 53 PCOS patients received the new treatment were compared to 32 PCOS patients treated with conventional methods. 5mg of Letrozole, 0.5mg of Cabergoline and 0.25mg of GnRH antagonist were administered from just after the oocyte pick up (OPU) for five consecutive days.

Results: There were no significant differences in the clinical pregnancy rate, cumulative pregnancy rate and cumulative live birth rate between the two COS. The number of days between OPU and menstruation start in the novel COS was significantly lower than that of the conventional one (5.26+2.59 vs. 17.62+5.75). This treatment produced no incidences of OHSS, compared to 21.9% of all cases having mild OHSS with the conventional method.

Conclusion: We found that administering Letrozole, Cabergoline and GnRH antagonist for five days consecutively after OPU effective for the complete prevention of OHSS.

Key Words: Cabergoline, letrozole, ovarian hyperstimulation syndrome, polycystic ovarian syndrome.

Received: 16th April 2022, **Accepted:** 29th June 2022

Corresponding Author: Atsushi Tanaka, Saint Mother Clinic, Department of Obstetrics and Gynecology, Kitakyushu, Japan, **Tel.:** +81-93-601-2000, **E-mail:** incho@stmother.com

ISSN: 2090-7265, August 2022, Vol.12, No. 3

INTRODUCTION

GnRH antagonist- agonist based COS, which is now widely used for PCOS, seems to be the best COS for PCOS even though it is accompanied with OHSS in up to 12% of all cases[1-5]. However, almost all of the studies on this topic reported the incidence of moderate to severe OHSS. The identification of most mild OHSS cases is unclear due to the lack of a unified classification of the severity of OHSS. The Cochrane Library reported only the incidence of severe OHSS with antagonist protocol [2.6% (54/2065)]. I assume there is a higher occurrence of mild or less than mild but still problematic OHSS. LOD is beneficial for treating PCOS, it decreases the number of antral follicles and lowers the frequency of OHSS. It produces spontaneous ovulation rates of 30-90% and total pregnancy rates of 13-88%[6]. However, it has the disadvantage of a short effective period of one year and occasionally the serious aftereffect of ovarian dysfunction due to aggressive cauterization.

IVM seems to be safe and effective treatment in terms of no occurrence of OHSS[7]. However, it has the disadvantage of lower clinical outcomes than those after using GnRH- based COS[8]. The epigenetic risks of ART using oocytes derived from IVM have not been resolved yet[9]. Considering the advantages and disadvantages of LOD and IVM as described above, the currently used GnRH antagonist-based COS is more likely to be chosen as the first-line treatment for PCOS. However, this COS, which consists of using GnRH antagonist for suppression of spontaneous LH surge during gonadotrophin

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administration and GnRH agonist as a trigger, showed the best clinical outcome except for the occurrence of OHSS in about 10% of the cases[1-5].

Our objective was to find a method that would eliminate or substantially reduce the incidence of OHSS found with current methods. We started a new treatment whose first part is similar to the conventional GnRH antagonist-based COS up to the point of oocyte pickup. We then add three kinds of medicine, Letrozole, Cabergoline and GnRH antagonist from right after the OPU and we continue the administration for five consecutive days. This new method eliminated incidences of OHSS, as defined by the Japan Society of Obstetrics and Gynecology (JSOG).

PATIENTS AND METHODS

Ethical Aspect

This new method was performed on patients who consented in writing to participate in this study at Saint Mother Clinic. The institutional Review Board of Saint Mother Clinic approved this study on August 6, 2019. The University Hospital Medical Information Network Clinical Trial Registry number was UMIN000045214.

Subjects

Ninety patients at St. Mother Clinic suffering polycystic ovarian syndrome participated in this study. Fifty-three women (55 cycles) received the novel COS between August 2019 and December 2021 and thirty-seven women (37 cycles) received the conventional one between January 2018 and June 2021. We used the Rotterdam criteria[10] for the definition of PCOS, that is having two out of the three following conditions:

1. Oligo-and/or anovulation.
2. Clinical and/or biochemical signs of hyperandrogenism.
3. Polycystic ovaries.

The main variable that was studied was the incidence of OHSS after administering the combination of the medication. In order the evaluate the quality of the ART intervention the following variables were also evaluated following standard procedures. Average age of patients, average level of anti-mullerian hormone (AMH), average total number of antral follicles (AFC), number of type 2 diabetes patients, average maximum level of E2, the average number of collected oocytes, cryopreservation rate and average number of frozen blastocysts, pregnancy rate, the cumulative pregnancy rate at one trial, miscarriage rate, live birth rate, cumulative live birth rate, gestational duration, and birth weight.

Comparison of the new treatment with conventional COS method

The novel treatment was evaluated retrospectively and compared with the conventional GnRH antagonist- based COS which is now most widely used.

Conventional GnRH antagonist protocol with GnRH agonist trigger (conventional COS)

We started with FSH (ASKA uFSH; ASKA Pharmaceutical Corporation) or HMG (FERRING HMG; Ferring Pharmaceuticals Corporation) injections, 150 IU/ml for 2 days followed by HMG injections, 150 IU/ml, until the trigger. GnRH antagonist 0.25mg shots (Cetrotide®; Nippon Kayaku Corporation) were started when the leading follicle reached 18 mm in diameter, and they were stopped when the largest follicle reached 22 mm, the GnRH agonist spray 900μg (Suprecur®; Sanofi Pharmaceuticals Corporation) was injected as trigger. All viable embryos were cryopreserved at the stage of blastocysts to avoid pregnancy during that cycle because of the high risk of OHSS. The frozen-thawed embryo was transferred in the next or two hormone replacement cycles later. The hormone replacement cycle was prepared by the combination of estrogen and progesterone administration. Estradiol tape (Estrana® tapes 0.72mg: Hisamitsu Pharmaceutical Company) was started from the 3rd day and its numbers increased gradually up to 6 tapes. Progesterone suppositories 300 mg (Lutinus® 100mg; Ferring Pharmaceuticals Company Limited) were applied when the endometrium reached more than 8 mm, embryos were transferred at 5 days after the start of progesterone suppositories.

Combined administration of three kinds of medicine from OPU for five days (Novel COS).

The procedure of the novel treatment is the same as the conventional one up to the oocyte collection except for the administration of Letrozole 2.5 – 5.0mg (Femara® tablet 2.5mg; Novartis Pharma) before trigger depending on the E2 level, and the use of GnRH agonist injection (Leuprorelin acetate 2mg: Lucrin® injection; AbbVie) as the trigger. We started to administer two tablets each of Letrozole and Cabergoline (Cabergoline 0.25mg; Sawai Pharmaceutical Corporation) and one tablet of GnRH antagonist (Relumina 40mg: ASKA Pharmaceutical Corporation) from immediately after OPU and continued for five consecutive days (Figure 1). All viable embryos were cryopreserved during that cycle and then the frozen-thawed embryo was transferred in the next or two hormone replaced cycles later which was the same as that of conventional COS. We checked all participating patients after 6 days after the OPU when all viable embryos' development was confirmed and monitored bilateral ovaries, severity of OHSS, abdominal symptoms and

measured the level of E2, P and VEGF. We recognize the severity of OHSS and its potential complications, so when we applied the novel method, we did so in a hospital setting that was prepared to handle potential complications or hospitalization. However, none of the patients had any symptoms that required emergency care or hospitalization.

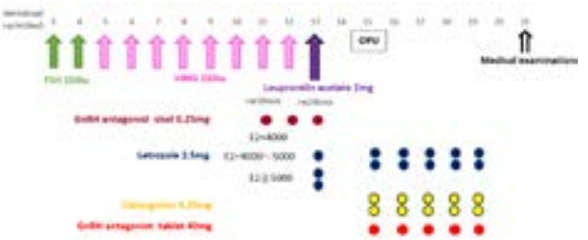

Fig. 1: Schema of novel ovarian stimulation protocol

Classification of OHSS

There are several OHSS severity classification criteria and there are considerable differences in the severity classification among different countries. We adopted the criteria set by the Japan Society of Obstetrics and Gynecology (JSOG). JSOG system classifies OHSS into three levels, mild, moderate, and severe. OHSS mild cases involve ovarian size 6-8 cm, ascites in minor pelvic cavity and normal result in biochemical examination. Ovarian size 8-12cm, ascites reaching upper abdomen and deteriorating trend of biochemical examination cases are classified as moderate, and cases when the diameter of ovary is > 12cm, there are ascites in total abdominal cavity and thoracic cavity, breathing difficulties, abdominal pain and abnormal data in biochemical examination are classified as severe. In our study ovarian size of four to five cm was observed in some of the patients, that is larger than normal size but short of the threshold to be classified as OHSS by the JSOG standards.

STATISTICAL ANALYSIS

Data were evaluated by chi-square test or Tukey-Kramer method and the difference was considered significant at the $p = 0.05$ level.

RESULTS

The clinical data obtained is as follows. The number of patients, average age of patients, average level of anti-mullerian hormone (AMH), average total number of antral follicles (AFC), number of type 2 diabetes patients, average maximum level of E2, the average number of collected oocytes, cryopreservation rate and average number of frozen blastocysts in novel COS and conventional one were (53, 37), (32.67 ± 4.03, 32.65 ± 3.47), (8.18 ± 4.16, 8.66 ± 2.94), (19.08 ± 8.08, 19.92 ± 5.00), (0% (0/53), 0% (0/37)), (4338.56 ± 2017.92, 4139.27 ± 1522.05), (23.09 ± 7.75, 24.03 ± 4.76), (96.4% (53/55), 100% (37/37)), (4.27 ± 3.46, 4.32 ± 2.68) respectively and no statistically significant differences were found between the two groups. Average number of days between OPU and menstruation in the novel COS was 5.26 ± 2.59 (range: 5–7 days) which was significantly shorter than in the conventional COS of 17.62 ± 5.75 days (Table 1).

Table 1: Comparison of clinical outcome between modified COS and conventional treatments -1

	Novel COS 53 women (55 cycles)	Conventional COS 37 women (37 cycles)	*p-value* (Novel COS vs Conventional COS)
Age*	32.67±4.03	32.65±3.47	0.98
AMH*	8.18±4.16	8.66±2.94	0.60
AFC*	19.08±8.08	19.92±5.00	0.55
Type 2 DM	0% (0/55)	0% (0/37)	N/A
Maximum E2 level (pg/ml)*	4338.56±2017.92	4193.27±1522.05	0.70
No. of collected oocytes*	23.09±7.75	24.03±4.76	0.48
Cryopreservation rate	96.36% (53/55)	100.0% (37/37)	0.24
No. of frozen embryos*	4.27±3.46	4.32±2.68	0.94
Days between OPU and menstruation*, ***	5.26±2.59	17.62±5.75	<0.001

* Mean ± standard deviation
** Total No. of G1+G2 / Total No. of collected oocytes, G1: completely matured oocytes, G2: almost completely matured oocytes
*** Days between oocyte pickup and menstruation start

No incidences of OHSS (mild/ moderate/ severe) were observed in the novel approach while the conventional COS had frequencies of 18.9% (7/37) (mild: 16.2% (6/37), moderate: 2.7% (1/37), severe: 0% (0/37)) (*p-values*, novel COS vs. conventional COS: <0.0001) (Table 2).

Table 2: Comparison of OHSS incidence between modified COS and conventional treatments

OHSS	Novel COS 53 women (55 cycles)	Conventional COS 37 women (37 cycles)	*p-value* (Novel COS vs Conventional COS)
Mild	0.0% (0/55)	16.2% (6/37)	0.002
Moderate	0.0% (0/55)	2.7% (1/37)	0.220
Severe	0.0% (0/55)	0.0% (0/37)	N/A
Total	0.0% (0/55)	18.9% (7/37)	<0.001

The clinical data of clinical pregnancy rate, the cumulative pregnancy rate at one trial, miscarriage rate, live birth rate, cumulative live birth rate, gestational duration and birth weight in novel COS and conventional one were [45.6% (41/90), 42.6% (26/61)], [71.7% (38/53), 56.8% (21/37)], [19.5% (8/41), 26.9% (7/26)], [32.2% (29/90), 29.5% (18/61)], [54.7% (29/53), 43.2% (16/37)], [39.31 ± 1.32, 39.00 ± 1.17], [3015.52 ± 285.35, 3032.63 ± 291.68], respectively and no statistically significant differences were found between the two groups (Table 3).

The average values ± standard error of VEGF in 20 cases at trigger day, OPU day, and 6th day after OPU were 120.08 ± 6.26 pg/ml, 131.69 ± 9.80 pg/ml, and 112.31 ± 5.75 pg/ml, respectively (*p-values*, Trigger point vs. OPU day: 0.34, Trigger point vs. 6th day after OPU: 0.38, OPU day vs. 6th day after OPU: 0.11) (Figure 2). Normal controls (The control average value ± standard error of VEGF was 134.30 ± 141.12 pg/ml among 18 women with an average age of 43.56 ± 3.54 years).

Table 3: Comparison of clinical outcome between modified COS and conventional treatments - 2

	Novel COS 53 women (55 cycles)	Conventional COS 37 women (37 cycles)	*p-value* (Novel COS vs Conventional COS)
Clinical pregnancy rate	45.6% (41/90)	42.6% (26/61)	0.72
Clinical pregnancy (n)*	38	21	N/A
Cumulative pregnancy rate	71.7% (38/53)	56.8% (21/37)	0.14
Miscarriage rate	19.5% (8/41)	26.9% (7/26)	0.48
Live birth rate	32.2% (29/90)	29.5% (18/61)	0.72
Cumulative live birth rate	54.7% (29/53)	43.2% (16/37)	0.28
On going	4	1	N/A
Gestational duration (wks)**	39.31±1.32	39.00±1.17	0.43
Birth weight (g)**	3015.52±285.35	17.62±5.75	<0.001

* Patients number
** Mean ± standard deviation

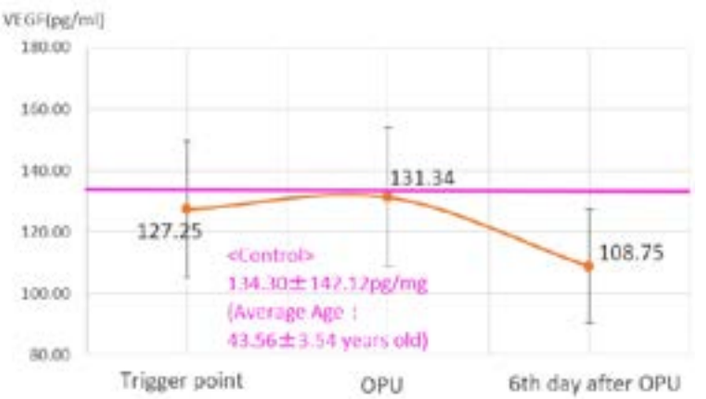

Fig. 2: The concentration of VEGF at three points

A successful case report following new COS

This is a report of one of the successful cases where the development of OHSS was prevented. After two shots of FSH 150 IU, HMG 150 IU × 6 was given. GnRH antagonist shot 0.25mg was given on 9th, 10th and 11th day leading follicle was φ23.7mm and E2 level was 6538 pg/ml on 11th day then Letrozole 2.5mg was administered and Leuprorelin acetate 2mg was given. Twenty-six oocytes were collected, and nine blastocysts were cryopreserved. Menstruation started 5 days after OPU (Figure 3).

The patient did not have any OHSS symptoms. The level of P, E2 and 6th days after OPU were 0.09pg/ml, <5 pg/ml respectively. The levels of VEGF at trigger, OPU and 6th day after OPU were 126 pg/ml, 271 pg/ml, 94.6 pg/ml (Figure 4). About 15 follicles each ovary was observed before OPU (Figure 5A). Almost all of follicles were aspirated and reduced in size right after OPU (Figure 5B). Both ovaries were decreased in one size smaller on second day after OPU (Figure 5C). Both ovaries ware not enlarged (44mm × 25mm, 45mm × 24mm). Activated corpus luteum characterized by hyperechoic angiogenesis was not observed by ultrasonic examination (Figure 5D). Echo free space found in Douglas pouch right after OPU (Figure 5E) was decreased on 2nd day after OPU (Figure 5F) and completely disappeared on 6th day after OPU (Figure 5G). A healthy baby was born following the frozen thawed embryo transfer in the hormone replaced cycle.

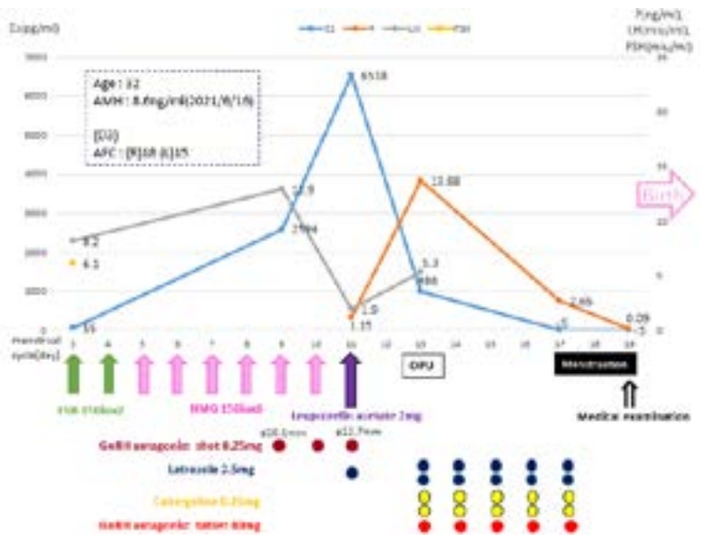

Fig. 3: A sample successful case report following novel COS

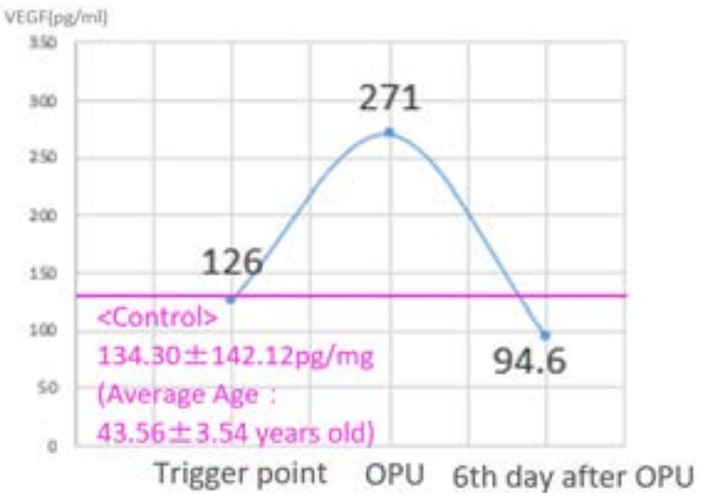

Fig. 4: Change of VEGF lelvels

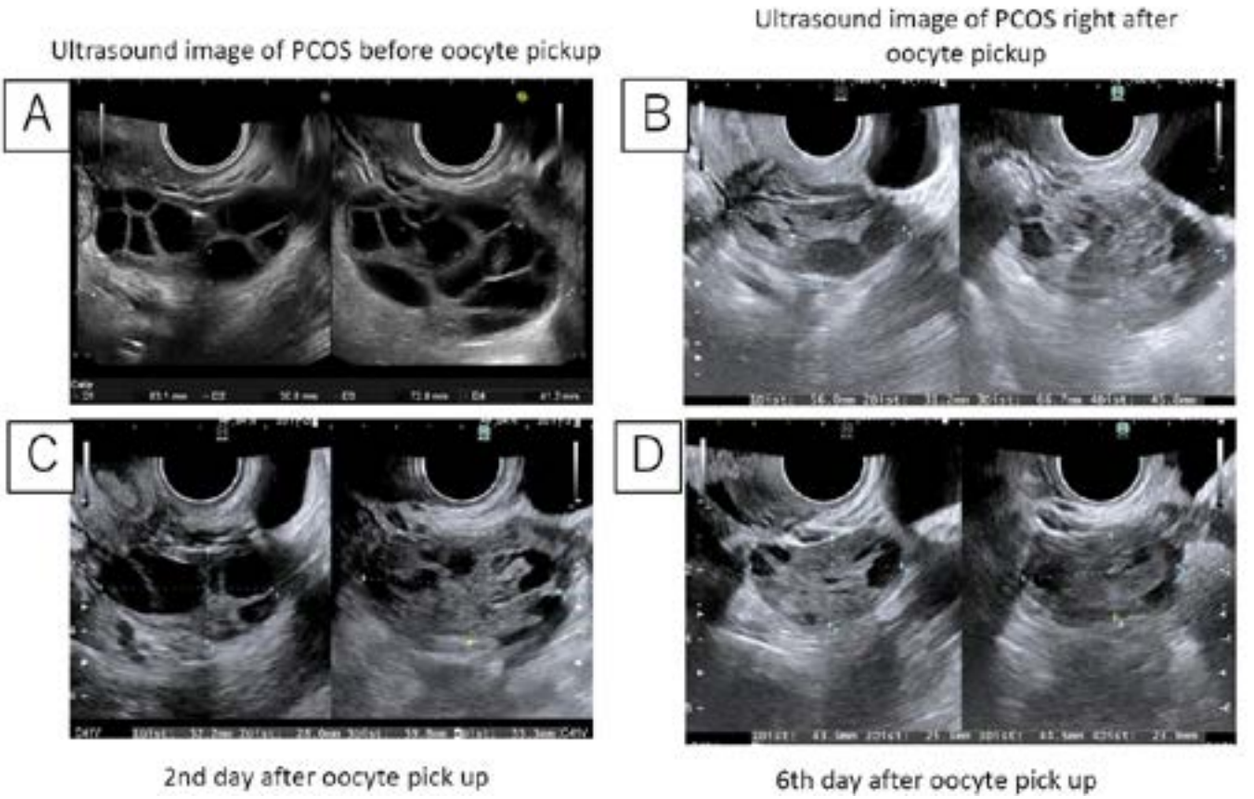

Fig. 5: Ultrasound image of bilateral ovaries in successful case using new treatment and Ultrasound image of echo free space in Douglas' pouch in successful case using new treatment.

DISCUSSION

PCOS is the typical cause of irregular ovarian function in young women and the biggest problem associated with COS is OHSS, which affects PCOS women. Multiple treatments have been tried to prevent OHSS. Low dose FSH administration, IVM[9,11-13], LOD[14] and Coasting[15] have been performed and achieved results that are only relatively successful because their clinical outcomes remain low when compared to patients with normal ovarian function[9,11].

How to control the incidence of OHSS that inevitably followed the treatment of PCOS was a major challenge that we needed to overcome. So, we started to do research to find a countermeasure to OHSS. Our goals for this new treatment were that it should be easy to perform, completely safe and reliable preventing OHSS. We tried to figure out how to stop the mechanism that produces OHSS. We looked for medicines that suppress the secretion of VEGF which in turn stimulates the angiogenesis in corpus luteum. We concluded that if we could stop the function of the corpus luteum and significantly decrease E2 and P levels the permeability of the veins would not increase leading to no occurrences of ascites. We found a highly effective treatment that completely prevented OHSS in the study participants.

Our method involves the combined use of three kinds of medicine; Letrozole, Cabergoline and GnRH antagonist tablet (Relugolix) that have their own independent anti-OHSS effects and created a synergetic effect when used together. Incidence of OHSS (mild, moderate, severe) after this administration were (0.0% (0/55), 0.0% (0/55), 0.0% (0/55)) compared to (18.8% (6/32), 3.1% (1/32), 0.0% (0/32)) in the conventional COS. However, some cases with slight enlargement of ovaries and slight abdominal uncomfortableness that did not reach the mild classification of OHSS were observed. The main reason of this improvement is thought to be the synergetic effect of the three kinds of medicine, when combined they inhibit the active angiogenesis in the corpus luteum resulting in the suppression of secretion of VEGF, Progesterone and Estradiol.

The idea of combining these drugs aiming at a synergetic effect for preventing OHSS was derived from four reports[16-19]. H.S. Lee reported that Letrozole has effects to reduce the E2 level without lower the quality of oocyte in GnRH antagonist base COS resulted in decreased risk of OHSS[18]. Y. Chen reported letrozole administration before the trigger shot of HCG in PCOS women lower the E2 level and incidence of OHSS due to luteolysis[16]. S.R. Soares reported co-administration of Cabergoline, and LH

or GnRH analogues have preventing effects for OHSS[17]. W.M. Ataallar and T.A. Elhamid evaluated the effect of Letrozole and Cabergoline for OHSS comparatively and reported that both have equally beneficial effect for prevention for OHSS[19]. Through this study we have found that the traditional approach of reducing the number and limiting the diameter of follicles should be reconsidered. We might not need to decrease the number of growing follicles. We were able to conduct usual COS for PCOS with no incidence of problematic OHSS and were able to obtain high quality oocytes.

The results of our study indicate that our novel treatment, GnRH antagonist-based COS using Letrozole, Cabergoline, and GnRH antagonist in combination, could completely prevent problematic development of OHSS and its application could be easily replicated to validate its efficacy. However, it is premature to conclude that this method has been established due to small case number in the current study. We need further investigation to validate the importance of this treatment to prevent problematic OHSS completely.

CONCLUSION

The timely and combined administration of Letrozole, Cabergoline and GnRH antagonist was effective at eliminating the OHSS risk that normally accompanies ovarian stimulation in PCOS patients. The suppression of angiogenesis in the luteum by the synergetic effect of the three medications seems to be the critical factor that allowed this level of success.

CONFLICT OF INTERESTS

There are no conflicts of interest.

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