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Half-dosage of gonadotropin-releasing hormone agonist is effective for pituitary desensitization during short IVF protocol.

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Abstract

Objectives: Gonadotropin-releasing Hormone agonists (GnRHa) has been used for pituitary desensitization during Controlled Ovarian Hyperstimulation (COH)-*In Vitro* Fertilization (IVF) for decades. We aimed to determine the clinical differences between half and full-dosage Leuprolide Acetate (LA) during short protocol COH-IVF.

Methods: All COH-IVF individuals were divided: (1) LA 0.5 mg/day (age<38, n=32); (2) LA 0.25 mg/day (age<38, n=38); (3) LA 0.5 mg/day (age ≥ 38, n=30); (4) LA 0.25 mg/day (age ≥ 38, n=33). The gonadropin dosage, Luteinizing Hormone (LH) surge, Ovarian Hyperstimulation Syndrome (OHSS) risk, oocyte and embryo number, Clinical Pregnancy Rate (CPR), and Live Birth Rate (LBR) were compared.

Results: We observed the non-significantly trends of lower gonadotropin dosages and higher LH surges in the half-dosage GnRHa groups compared to full-dosage GnRHa groups. Gonadotropin dosages (IU)/E2 (pg/mL) on human Chorionic Gonadotropin (hCG) day/LH surges in each group were: (1) 1454.4/1653.6/0%; (2) 1419.6/1683.5/3%; (3) 1954.5/910.8%/0%; and (4) 1893.5/953.6/3.7% respectively. The oocyte number, day 3 embryo number, OHSS, and CPR, LBR were non-statistically different between full and half LA groups. The oocyte number/day 3 grade I, II embryo number/CPR/LBR in each group were: (1) 11.3/5.6/37.5%/31.3%; (2) 11.8/5.1/39.4%/33.3%, (3) 6.5/2.6/19.2%/11.5%; and (4) 6.8/2.7/22.2%/14.8%.

Conclusions: Half-dosage GnRHa application results in comparable pituitary suppression and clinical outcomes compared to full-dosage GnRHa during short IVF protocol. The real roles of lower-dosage GnRHa upon pituitary desensitization during IVF warrant further investigation.

Keywords: COH, Gonadotropin-releasing hormone agonist, GnRHa, IVF, Pituitary down-regulation.

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Introduction

During the past decades, Gonadotropin-releasing Hormone agonists (GnRHa) have been widely used for pituitary desensitization during COH. Two GnRHa agents have been applied in pituitary depression during COH, including short and long regimens. The major concerns over long-acting GnRH depot preparations existed upon its profound suppression and luteal phase defects, which adversely affect pregnancy and miscarriage rates [1]. Furthermore, its large consumption of gonadotropins and longer COH period compared to short regimen are another concern [2]. Therefore, the short-acting GnRH agonist LA is currently widely used for pituitary suppression instead of the long-acting GnRHa.

Traditionally, there were two protocols of GnRHa upon pituitary suppression during COH, including short and long protocols. The main advantage of the short protocol of GnRHa is its greater convenience as well as its use is less stressful and more acceptable than that of long LA protocols. These years, widely application of GnRH

antagonist (GnRHant) upon COH-IVF has been reported. GnRHant protocol might be associated with lesser gonadotropin consumption and fewer injections than those in the GnRHa protocol for full responders [3]. Therefore, the GnRHant protocol is widely considered more cost effective and patient friendly than the GnRHa protocol [4].

However, recently report demonstrated the drawback of GnRHant upon the COH [5]. Some recent meta-analysis revealed that the GnRHant protocol is correlated with a higher cancellation rate due to poor ovarian response compared with the GnRHa protocol [6], especially in patients with<4 oocytes in previous COH cycles [7] and in patients with expected poor ovarian response [8], thereby raising the concerns about its effectiveness in poor ovarian responders. Since GnRHa protocol might be more effective than GnRHant protocol for patients with Diminished Ovarian Reserve (DOR). The further reevaluation of GnRHa upon COH-IVF might be merited.

In general, Asian women are thinner than Caucasian women. Given the racial and ethnic differences, it is logical to suspect that Asians and Caucasians might have different effective GnRHa dosages. To select a more efficient protocol for GnRHa for IVF patients, we designed this randomized study to evaluate the follicular development and pregnancy outcome using different dosage protocols for GnRHa. We aimed to determine whether the half-dose GnRHa is feasible during short IVF protocol in thin Asian women and evaluated its risk during pituitary down-regulation. Furthermore, we also compared the clinical differences between full and half-dosage of GnRHa upon IVF-ET. To our knowledge, this is among the first few comparisons of these protocols in Asian population.

Materials and Methods

All patients who received COH with short protocol of LA (0.5 mg or 0.25 mg/day subcutaneously; Abbott Laboratories, Chicago, IL, USA), IVF/Intracytoplasmic Sperm Injection (ICSI) and Transvaginal Embryo Transfer (TV-ET) between 2016 and 2022 were recruited. This trial was a phase III, open label, randomized study to assess the efficacy and safety of different dosage of LA in women undergoing COH. The main inclusion criteria were: Age between 20-45 years and body weight of 40-80 kg. The study was approved by the Hsieh Women Clinics Ethic Committee (HWC-20240412).

The details of application were presented as previous reports [9]. The patients were divided into four groups: (1) LA 0.5 mg/day (age<38, n=32); (2) LA 0.25 mg/day (age<38, n=38); (3) LA 0.5 mg/day (age ≥ 38, n=30); (4) LA 0.25 mg/day (age ≥ 38, n=33). The short protocol of LA administration in each group were started since menstrual day 2-3 till the day of hCG administration. The COH protocol was the same as in our previous report [10]. In brief, during menstrual days 2-7, younger patients (<34 years) were administered 150-225 IU/day of recombinant Follicle Stimulating Hormone (FSH) (Gonal-F; Serono, Rome, Italy). Older patients (≥34 years) were administered 225-300 IU/day of Gonal-F.

The hCG (5,000 IU; Serono, Rome, Italy) was administered until two or more follicles of ≥ 18 mm were detected. Serum LH and E2 concentrations were tested on the day of hCG administration. Oocytes were retrieved transvaginally 34-36 hours later. Oocyte culture, insemination, Embryo Transfer (ET) and cryopreservation were as previously described [10]. ET was performed 72 hours after oocyte retrieval. A maximum of four embryos were transferred in each patient.

Luteal phase was supported with hCG (2,000 IU/day; Serono, Rome, Italy) on days 1, 4 and 7 post-ET and progesterone (600 mg/day; Utrogeston) after oocyte retrievals. Chemical pregnancy was defined as elevated serum β-hCG (above 50 IU/L) 14 days after ET.

Clinical pregnancy was determined by visualization of a gestational sac, and fetal viability by ultrasound 4 weeks post-ET. Personal data (age, body weight, body mass index, cause of infertility), Gn dosage, and serum concentration of LH and E2 on the day of hCG administration were compared between each group. Retrieved oocyte and embryo numbers, development of OHSS, embryo quality, and Pregnancy Rate (PR), Implantation Rate (IR) and Abortion Rate (AR) in each group were compared. The SAS system version 8.1 (SAS Institute Inc., Cary, NC, USA) with ANOVA test were used for statistical analysis. A P<0.05 was considered statistically significant.

Results

The body mass index and the indications for IVF treatment were comparable between each group (Table 1). The age between full and half-dosage LA groups were also non-significantly. The non-significant trends of lower gonadotropin dosages in the half-dosage GnRHa groups compared to full-dosage GnRHa groups were observed.

The non-significantly trends of higher LH surges and lower OHSS risk were also noted in the half-dosage GnRHa groups compared to the full-dosage GnRHa groups. The LH surge/OHSS risks in each group were also comparable. Gonadotropin dosages (IU)/E2 levels (pg/mL)/LH surges/OHSS in each group were: (1) 1454.4/1653.6/0%; (2) 1419.6/1683.5/3%, (3) 1954.5/910.8%/0%; and (4) 1893.5/953.6/3.7% respectively (Table 2).

There were no significant differences in clinical outcomes between full and half-dosage LA (group 1 *vs.* 2 and group 3 *vs.* 4). The numbers of oocytes and /day3 grade I, II embryos were comparable between full and half-dosage LA groups.

The OHSS risk, CPR, and LBR were not statistically different between full & half LA dosage groups. The oocyte number/day3 grade I, II embryo number/CPR/LBR in each group were: (1) 11.3/5.6/37.5%/31.3%; (2) 11.8/5.1/39.4%/33.3%; (3) 6.5/2.6/19.2%/11.5%; and (4) 6.8/2.7/22.2%/14.8% respectively (Table 2).

Table 1. *Personal data for patients who received full and half-dosages of LA for pituitary suppression during COH*[*]*.*

	LA 0.5 mg/day (age<38, n=32) (group 1)	LA 0.25 mg/day, (age<38, n=33) (group 2)	LA 0.5 mg/day (age ≥ 38, n=26) (group 3)	LA 0.25 mg/day (age ≥ 38, n=27) (group 4)
Age (year)	33.5 ± 3.2[†]	33.6 ± 3.1[†]	40.6 ± 1.1[‡]	40.8 ± 1.5[‡]
BMI (Kg/m²)[§]	21.9 ± 2.4[†]	21.5 ± 2.0[†]	22.3 ± 2.5[‡]	22.7 ± 2.1[‡]
Infertility causes[§]	DOG1	DOG1	DOG1	DOG1
Tubal factor	4 (12.5)	6 (18.2)	5 (19.2)	3 (11.1)
Male factor	15 (46.9)	16 (48.5)	14 (53.9)	15 (55.6)
Endometriosis	5 (15.6)	4 (12.1)	3 (11.5)	4 (14.8)
Idiopathic	5 (15.6)	5 (15.1)	3 (11.5)	3 (11.1)
Others	3 (9.4)	2 (6.1)	1 (3.9)	2 (7.4)

Note: [*]Data are presented as mean ± standard deviation or number (%); [†]Non-significant difference between group 1 *vs.* group 2; [‡]Non-significant difference between group 3 *vs.* group 4 and [§]Non-significant difference between each group and BMI: Body Mass Index.

Table 2. *Clinical results and laboratory data for patients who received different dosages of LA for pituitary suppression during COH*[*]*.*

	LA 0.5 mg/day (age<38, n=32) (group 1)	LA 0.25 mg/day (age<38, n=33) (group 2)	LA 0.5 mg/day (age ≥ 38, n=26) (group 3)	LA 0.25 mg/day (age ≥ 38, n=27) (group 4)
Gonadotropin dosage (IU)	1454.4 ± 288.7[†]	1419.6 ± 209.3[†]	1954.5 ± 328.4[‡]	1893.5 ± 386.4[‡]
E2 (pg/mL) on hCG day	1653.6 ± 259.1[†]	1683.5 ± 267.7[†]	910.8 ± 179.1[‡]	953.6 ± 189.7[‡]
LH surge[§]	0	1 (3)	0	1 (3.7)
OHSS	3 (9.4)[†]	4 (12.1)[†]	0[‡]	0[‡]
Oocyte	11.3 ± 3.5[†]	11.8 ± 3.1[†]	6.5 ± 2.1[‡]	6.8 ± 1.7[‡]
Embryo	8.5 ± 2.7[†]	8.7 ± 2.5[†]	4.2 ± 1.5[‡]	4.1 ± 1.1[‡]
D3 grade I/II embryo	5.6 ± 1.8[†]	5.1 ± 1.7[†]	2.6 ± 0.8[‡]	2.7 ± 0.7[‡]
Chemical pregnancy rate	12 (37.5)[†]	13 (39.4)[†]	5 (19.2)[‡]	6 (22.2)[‡]
Live birth rate	10 (31.3)[†]	11 (33.3)[†]	3 (11.5)[‡]	4 (14.8)[‡]

Note: [*]Data are presented as mean ± standard deviation or number (%); [†]Non-significant difference between group 1 *vs.* group 2; [‡]Non-significant difference between group 3 *vs.* group 4; [§]Non-significant difference between each group; E2: Estradiol; FSH: Follicle-Stimulating Hormone; LH: Luteinizing and OHSS: Ovarian Hyperstimulation Syndrome.

Discussion

Selection of adequate COH protocol is critical for clinical IVF approaches. Pituitary down-regulation is one inevitable step during COH, which is essential for the better recovery of a larger number of oocytes, prevention of premature LH surge, luteinisation, and a lower cycle cancellation rate. Currently, there are three major regimens for pituitary desensitization, including, GnRHa, GnRH antagonist, and progesterone. Over the last three decades, GnRHa was the most commonly used drugs for COH in assisted reproductive procedures. GnRHa have been long-term used for pituitary suppression to avoid the adverse effect of a premature LH surge [10]. The use of a GnRHa for IVF cycles significantly reduced the cycle cancellation rate and improved the ovarian response [11].

Different dosages and formulations of GnRHa have been devised. The advantages of GnRHa in COH/IVF-ET using the "short protocol" have been well known [12]. In reviewing the MEDLINE database, few investigators have studied the clinical effects of lowering the dose of short-acting GnRHa. No studies report trials of lower dosage of GnRHa in Asians. Recently, Walker *et al*., [13] demonstrated that lower dosage of GnRHa protocols were effective for preventing the LH surge, and resulted in similar PR in individuals with DOR. They even decreased the LA dosage to the 0.2 mg, 0.1 mg and 0.05 daily in these individuals with Patient-Oriented Strategy Encompassing IndividualizeD Oocyte Number (POSEIDON) classification groups 3 and 4. Scanty literature has dealt with the use of lower GnRHa doses in pituitary suppression of patients with normal ovarian deserves.

Embryo quality or euploid rates are the essential consideration of the COH protocols for ART clinicians. The suppression by larger-dosage of GnRHa might interrupt the folliculogenesis and decrease serum E2 elevation. It is logical to suspect that the decreased dosage of GnRHa might be useful for the decreasing of the related

risk. Larger dosage LA administration might result in greater suppression of LH, which produces lower serum levels of E2 when gonadotrophins devoid of LH are used [14]. Some LH supplement might need to be considered during COH. LH is effective in stimulating E2 secretion in granulosa cells that have acquired LH-binding sites [15]. The addition of recombinant LH might prevent a decrease in estradiol during pituitary desensitization [16]. Therefore, minimal dose adjustment of GnRHa to suppress LH release without impairing the oocyte development and embryo implantation might be considered in these situations.

The major drawback of GnRH depot is its induced profound pituitary and ovarian suppression during COH. Therefore, in our previous study, we demonstrated that 1.88 mg instead of 3.75 mg GnRHa depot is an adequate dosage for pituitary suppression [10]. We found that the use of low-dose GnRHa depot had the advantages of convenience, less stress and being cost-effective [9]. Therefore, it is logical to suspect this lower adjustment dosage of short-acting GnRHa would also apply for pituitary suppression in Asians. Major advantages of short protocol of GnRHa include a shorter duration of COH, reduced dosage of gonadotrophin, and a lower risk of OHSS compared with GnRH depot [9].

Compared to the GnRHa short protocol, the long protocol of GnRHa from the previous luteal phase is inconvenient, tiring and stressful. The short protocol GnRHa, by either injection or intranasal spray, can provide simple treatment in women undergoing COH, achieving comparable PR compared with the long protocol regimen. In current practices, both GnRHa and GnRH antagonist are routinely used to suppress endogenous gonadotropins during IVF treatment. Despite the convenience of GnRHant, the GnRHa administration is still widely adapted. There is still controversy about the real efficacy of GnRH-ant administration. Some investigators claimed that an equivalent PR was achievable using GnRHant protocols and GnRHa protocols [17]. In contrast, some investigators demonstrated lower levels of serum E2, fewer small follicles/oocyte and decreased PR in GnRH-ant cycles, when compared with GnRHa [18]. In contrast, some investigators demonstrated lower levels of serum E2, fewer small follicles/oocyte and decreased PR in GnRH-ant cycles, when compared with GnRHa [18].

A recent meta-analysis revealed that the GnRHant protocol is correlated with a higher cancellation rate compared with the GnRHa protocol [6], especially in patients with DOR [8]. GnRHant injection during the early follicular phase would likely disturb the growth of cohort follicles [19]. In several trials, the GnRHant regimens have been associated with slightly lower PR and IR than the established GnRHa protocols [20]. Since several studies have indicated a slight reduction in PRs with GnRHant, developing flexible regimens with GnRHa in some individual patients is warrant [21].

In our previous survey, we demonstrated the lowest effective dosage of GnRHant (cetrorelix) for pituitary desensitization during COH luteolysis is 0.25 mg, resulting in a comparable PR but a higher AR when compared with GnRHa [9]. Since the lower dosage of GnRH depot and GnRHant have been reported to apply in normal IVF individuals, it is logical to suspect the decreased dosage of GnRHa might prevent the over status of hypogonadotropic and hypogonadal condition. Furthermore, the higher gonadotropin consumption was also observed in the GnRHa regimen, compared to the GnRHant protocol [5]. The half-dosage GnRHa application might decrease the related consumption of gonadotrophins.

Recently, some reports demonstrated that the GnRHa protocol was associated with a low ET cancellation rate, high implantation rate and high LBR, compared to the traditional GnRHant protocols [5]. The GnRHa protocol might be more effective than the GnRHant protocol for patients with DOR [5]. The GnRHa application is associated with of lower ET cancellation rates, higher implantation rates, and higher LBR, compared to GnRHant group [5]. However, these comparisons existed of GnRHa with full-dosage and long protocol with GnRH antagonist. It is suggested that GnRHa have a direct effect on ovarian steroidogenesis, which is independent of their action on the pituitary [22].

Another concern is that pituitary down-regulation might impair the corpus luteum function in IVF cycle [23]. Inadequate COH protocol might elevate the progesterone levels as well as interrupt the ovarian statuses or endometrial maturation in the late follicular and subsequent luteal phase. There was non-significant difference in pre-retrieval serial serum progesterone levels and luteal phase endometrial histology existed between cycles utilizing GnRHa or GnRHant [24]. Luteal support is essential when a long-acting GnRHa is used [25]. Adequate luteal support compensates for luteolysis induced by GnRHa or GnRHant and assures good clinical outcome. Some hCG addition after ET is useful to preserve corpus luteum function [25]. In our unit, we routinely administer 1,500 IU of hCG on days 1, 3 and 5 post-ET, to prevent the negative effects of GnRHa or GnRH-ant on the corpus luteum or the endometrium. The reduced-dose GnRHa might decrease the demand of the luteal support as well as resulting similar clinical results.

It is still controversial about the body weight influences upon the GnRHa or GnRHant dosage during COH. Engel *et al*., [26] demonstrated that body weight did not influence GnRHant plasma concentrations. They suggested that GnRHant modification was unnecessary for individuals with different body weights during COH. In contrast, Al-Inany *et al*., [27] reported that serum levels of GnRHant exhibited a linear inverse relationship to body weight. They indicated that smaller women would probably require lower doses of GnRHant for preventing the LH surge. However, the related literature about the

body weight influences upon GnRHa dosage adjustment is scanty. Concerning racial differences, most Asian women appeared to be thinner than Caucasians. The decreasing dosage of GnRHa might be priory used in the individuals with normal body weight.

In our clinical trials, there were only two cases with LH surge under half-dosage GnRHa protocol in young and older individuals. We observed the LH surge risk might be higher in the cases with larger BMI. The daily following-up of urine LH surge should be adopted in these high-risk patients. We adapted the addition of half-dosage GnRHant for preventing the advent of LH suerge. We found the premature ovulation could be completely prevented after the additional half-dosage GnRHant administration.

In this series, to the best of our knowledge, we demonstrated the first application of half-dosage of GnRHa in Asians with both normal and diminished ovarian function. We observed the comparable results with that of traditional full-dosage GnRHa. We observed the borderline lower gonadotrophin consumption, higher E2 levels, higher OHSS rates, and higher LH suge in the half LA groups. Embryo qualities did not significantly differ between the two protocols. On the basis of these results, when the convenience, costs and side-effects are taken into account, a half-dose GnRHa might be preferable. It also suggests that lower-dosage GnRHa applications might be priory considered in the IVF individuals with DOR and thinner BMI. As clinicians might gain experience with larger applications of lower-dosage GnRHa. The optimal treatment paradigms will likely emerge.

Half-dosage GnRHa application results in comparable pituitary suppression and favourable clinical outcomes compared to full-dosage GnRHa during short IVF protocol.

Conclusion

In conclusion, half-dosage GnRHa regimen results in comparable pituitary suppression and clinical outcomes compared to full-dosage GnRHa during short IVF protocol. The application of half-dosage GnRHa is feasible upon individuals with normal body weights and ovarian reserves. Further application of lower dosage GnRHa regimen might allow short and simple treatment strategies for IVF patients undergoing COH. It might be expected that the low-dosage GnRHa might lead to a shorter, cheaper and safer protocol. Clinical outcomes might be improved by developing more flexible LA dosage regimens.

Additional large scale randomized trials are required to confirm our findings. Furthermore, the influence of different dosage of GnRHa upon the folliculogenesis, luteolysis, follicular synchronization, and endometrial statuses during luteal phase merits further study. The embryo euploid rates, oocyte and embryo qualities, blastocyst formation ratios as well as implantation and pregnancy rates of different GnRHa dosage protocols warrant further investigation.

Conflict of Interest

Authors declare there are no conflict and competing interests.

Acknowledgement

Data regarding any of the subjects in the study has not been previously published unless specified. Data will be made available to the editors of the journal for review or query upon request. Consent for publication, availability of data and material and code availability were obtained before the series surveys. The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Ethical Approval

Approval from the institutional review board and ethics were obtained for the analyses of this series. Consent to participate were obtained before the applications of this series. The subjects in this trial have not concomitantly been involved in other randomized trials.

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