Evaluating Body Weight In Predicting Initial Gn Dosage During IVF For Women With PCOS: A Retrospective Study

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Research Article

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Abstract

Background: Polycystic ovarian syndrome (PCOS) is the major cause of anovulatory infertility. Since women with PCOS are often accompanied by increased body weight and infertility, Individualized gonadotropin (Gn) dose is required to achieve therapeutic effect while minimizing the risk of ovarian hyperstimulation simultaneously. We aimed to investigate the essential role of body weight in optimizing initial Gn dosage for PCOS patients during in vitro fertilization (IVF).

Methods: We retrospectively included 227 infertile PCOS patients who used gonadotropin-releasing hormone (GnRH)-antagonist fixed protocol underwent their first cycle of IVF in West China Second University Hospital from January 2019 to December 2020. Baseline characteristics controlled ovarian stimulation parameters, and reproductive outcomes were compared between patients with different body weights and different ovarian responses. Multivariable logistic regression analyses were adopted to investigate the relationship between body weight and initial Gn dosage. Receiver operating characteristic (ROC) curves were drawn to find the optimal cut-off value of body weight in predicting the starting Gn dosage so as to prevent high ovarian response (HOR).

Results: Circulating testosterone (T) level was increased and Anti-Mullerian hormone (AMH) level was decreased in higher weight groups compared to lower weight groups. Increased body weight was significantly correlated to the rise of initial Gn dosage (OR = 1.113, 95% CI = 1.021-1.227, p = 0.016). Normal ovarian response (NOR) patients had significantly less fresh cycle cancel rate and ovarian hyperstimulation syndrome (OHSS) rate which outweighed the slightly fewer embryos compared with HOR patients. Using ROC curves, 55.5 kg and 70.5 kg were identified as the optimal cut-off values to predict the initial Gn dosage no more than 150 IU (sensitivity, 72.5%; specificity, 63.4%) and 225 IU (sensitivity, 75.0%; specificity, 95.2%), respectively.

Conclusion: Body weight was an independent factor for initial Gn dosage. Adjusting initial Gn dosage based on body weight is crucial to achieving better reproductive outcomes for PCOS patients during IVF.

Background

Polycystic ovarian syndrome (PCOS), a complex and multifaceted disorder characterized by hyperandrogenism, ovulatory dysfunction, and polycystic ovaries, has an increasing incidence rate of 4.47% and an age-standardized incidence rate of 1.45% per year globally[1]. Approximately half of the PCOS patients are overweight or obese[2] and obesity plays an important role in the pathogenesis of PCOS and may aggravate the adverse metabolic outcomes of PCOS[3]. About three-quarters of PCOS patients suffered from another common complication, infertility, making PCOS the major cause of anovulatory infertility[4]. Assisted reproduction technology (ART), including in vitro fertilization (IVF) and embryo transfer (ET) and intracytoplasmic sperm injection (ICSI), is often needed when patients are resistant to ovarian induction or complicated with other infertility factors.

Women with PCOS exhibit higher sensibility and exaggerated response to gonadotropins which could result in an increased risk of ovarian hyperstimulation. Ovarian hyperstimulation syndrome (OHSS) is a serious iatrogenic complication characterized by fluid shifting from intravascular to extravascular spaces due to arteriolar vasodilatation and increased capillary permeability[5]. It occurs as mild type in 20-30% IVF cycles and may develop to moderate or severe type in 2-3% cycles[6]. Individualized exogenous gonadotropin (Gn) dose is essential for minimizing OHSS risk and optimizing follicle recruitment at the same time. The strategies to manage OHSS include initial dosage selection and dose adjustment during cycle[7]. Several studies have developed a series of algorithms to predict the proper initial dosage of Gn based on age, Anti-Mullerian hormone (AMH), body mass index (BMI), baseline follicle stimulating hormone (FSH) level or ovarian response of the previous cycle[8-11]. Obesity also takes an essential part in ovarian

response and could augment adverse reproductive outcomes[3]. However, these studies were lack of evidence-based on body weight and regimens aimed at PCOS patients were limited.

Body weight is one of the factors associated with pharmacokinetic parameters. Patients with different body wight require dose adjustment to achieve equivalent therapeutic effects. Some had reported that body weight is more important than BMI in determining the dosage of exogenous Gn[12]. Studies have found that body weight was negatively associated with exogenous Gn levels[12, 13]. Abbara and colleagues reported that weight-adjusted rFSH dose could predict follicular growth and retrieval in general women, while the complications and pregnancy outcomes were not reported[14]. As a large number of PCOS patients are accompanied by increased body weight, up-regulating Gn dose is often needed to achieve the therapeutic effect, however, which in turn may increase the risk of ovarian hyperstimulation. Therefore, it is important to weigh the pros and cons and find the balance when adjusting Gn dose according to body weight.

In this retrospective cohort study, we aimed to investigate the association between body weight and individualized Gn dosage and the ART outcomes in women with PCOS undergoing IVF cycles. In addition, we tried to find the optimal cut-off value of body weight in predicting the initial Gn dosage in PCOS patients in order to prevent high ovarian response (HOR).

Methods

Study population

In this study, we retrospectively enrolled infertile patients diagnosed with PCOS who underwent their first cycle of IVF in Reproductive Center, Department of obstetrics and gynecology, West China Second University Hospital from January 2019 to December 2020. The Ethical Review Board of West China Second University Hospital, Sichuan University approved the study and waived the need for written informed consent (Approval No. 2021-033). The data was handled and analyzed anonymously.

PCOS was diagnosed according to the European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine (ESHRE/ASRM) (Rotterdam criteria)[15]. Only the first controlled ovarian stimulation (COS) cycles treated with gonadotropin-releasing hormone (GnRH)-antagonist fixed protocol was included. Exclusion criteria include: male factor infertility, other COS protocols (i.e. GnRH-antagonist flexible protocol, depot GnRH-agonist protocol, long GnRH-agonist protocol, etc); second or further COS cycles; female with any known systemic or endocrine diseases, such as Cushing syndrome, androgen secreting ovarian tumors or adrenal tumors, functional hypothalamic amenorrhea (FHA), thyroid diseases, hyperprolactinemia, premature ovarian insufficiency (POI); couples with abnormal chromosome karyotype not including chromosome polymorphisms; female with a history of recurrent spontaneous abortion.

Baseline clinical characteristics including age, type of infertility, oligo/hypomenorrhea, height, weight, BMI (kg/m2) were extracted from the patient records. Laboratory examination data including baseline testosterone (T) level (ng/ml), dehydroepiandrosterone sulfate (DHEAS) level (ug/dl), androstadienone (AND) level (ng/ml), sex hormone-binding globulin (SHBG) level (nmol/L), FSH level (IU/L), luteinizing hormone (LH) level (IU/L), antral follicle count (AFC) level, and AMH level (ng/ml) were also collected. Sex hormones and AFC were measured on Day 2-4 of the menstrual cycle.

Controlled ovarian stimulation protocols

As mentioned above, only patients who were treated with fixed GnRH-antagonist protocol were included in this study. Briefly, exogenous Gn (Gonal-F, Merck Serono, Germany; or Urofollitropin for Injection, Livzon Pharmaceutical Group Inc., China; or PUREGON, Merck Sharp & Dohme B.V., Canada; or Follitropin, GeneScience Pharmaceuticals Co., Ltd., China; or Menopur, Ferring GmbH, Germany), generally 100-375 IU/day, was administered starting from day 2-3 of menstruation. The doses were individualized based on the patient's age, BMI, AFC and follicular response. GnRH-antagonist (Cetrotide, 0.25 mg, QD Merck Serono, Germany) was daily administrated after 5-7 days usage of Gn and the administration of GnRH-antagonist continued until triggering. Urine human chorionic gonadotropin (hCG) (Ovidrel; 8000-10000 U; Merck-Serono, Germany) was given to trigger ovulation when two leading follicles reached a mean diameter of 18 mm, or three follicles reached a mean diameter of 17 mm. A decreased dose of urine hCG (5000 IU), recombinant hCG (250 ug), or GnRH agonist (0.2 mg) with urine hCG (2000 IU) was used to trigger ovulation when patients were at high risk of OHSS. Initial Gn dosage (IU/day), stimulation time (days), total Gn dosage (IU), number of oocytes with diameter ≥14 mm on trigger day, estradiol (E2) on trigger day (pg/ml), progesterone (P) on trigger day (ng/ml), LH on trigger day (IU/L), and endometrial thickness on trigger day (mm) measured by sonographic examinations were recorded. Ovarian sensitivity index (OSI) was calculated by dividing the total dosage of Gn by the number of oocytes retrieved.

Fresh embryo transfer cycle

Oocytes were retrieved transvaginally 36-38 h after the trigger. If the patients showed increased progesterone level or at high risk of OHSS, fresh ET cancellation and freeze-all strategy were applied. All the additional embryos were cryopreserved. The morphology of embryo or blastocyst was assessed to determine its quality [16]. The Day 3 embryo was defined as good-quality if it presented 2 pronuclei (PN) when fertilization, had six to ten blastomeres and no more than 20% fragmentation. The blastocyst was defined as good-quality if it met with the inner cell mass/trophectoderm score of AA, AB, BA or BB.

In the present study, data including oocytes retrieval, mature oocytes, number of D3 embryos and blastocysts, fresh ET cancellation rate, and clinical pregnancy rate were collected. HOR was defined as a patient who had at least one of the following features[17]: (1) >15 retrieved oocytes during COS cycle; (2) > 20 oocytes larger than 12-14mm in diameter during COS cycle; (3) cycle cancellation due to excessive follicular development; (4) E2 > 5000 ng/l during COS; (5) moderate or severe OHSS after COS. Poor ovarian response (POR) was defined as ≤ 3 retrieved oocytes[18]. And the rest was defined as the normal ovarian response (NOR). Serum hCG test was conducted 14 days after ET and transvaginal ultrasound (TVS) was done 28 days after ET. Clinical pregnancy was recorded when the gestational sac was observed by TVS. Patients who were hospitalized because of severe OHSS were recorded.

Statistical analysis

We first divided the participants into four groups based on body weight: body weight between 40-50 kg (Group A), body weight between 50-60 kg (Group B), body weight between 60-70 kg (Group C), and body weight greater than 70 kg (Group D). Continuous variables were expressed as mean ± standard deviation (SD) and category variables were displayed as frequency (n) and percentage (%). One-way analysis of variance (ANOVA) test was applied to compare continuous variables between the four groups and LSD test was used as the post hoc test (also known as the multiple comparison test), Chi-square test and/or Fisher's exact test was used for the comparison between the four groups as appropriate, and Bonferroni correction was used for comparison between every two groups. Multivariable logistic regression analyses were also performed to compare the set-up of initial Gn dosage (>150 IU/day). Age, weight, BMI, T, and AMH were adjusted in the logistic regression model. Odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) were determined for both the non-adjusted model and the adjusted model. Afterwards, we compared the reproductive outcomes between PCOS patients with HOR and NOR. While the student's t-test was adopted for the

comparison between the two groups, Chi-square test and/or Fisher's exact test was used to compare category variables between the aforementioned two groups. A receiver operating characteristic (ROC) curve was used to identify a cut-off value for body weight to accurately predict the need of limiting initial Gn dosage. The optimized cut-off value was selected where the ROC curve reached the maximum area under curve (AUC) with the greatest sum of sensitivity and specificity.

For all comparisons, a two-sided p-value < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 22.0 (IBM, Armonk, NY, USA).

Results

Baseline characteristics

A total of 227 women diagnosed with PCOS who used GnRH-antagonist fixed protocol as COS protocol were included in the present study. The BMI (Group A = 18.6 ± 1.49, Group B = 21.47 ± 1.52, Group C = 24.94 ± 1.59, Group D = 28.33 ± 2.09, p < 0.001) and circulating T level (Group A = 0.47 ± 0.18, Group B = 0.44 ± 0.17, Group C = 0.49 ± 0.22, Group D = 0.83 ± 1.33, p = 0.003) were increased in higher weight groups compared to lower weight groups. Also, compared with patients in higher weight groups, those in lower weight groups had significantly higher level of AMH (Group A = 11.99 ± 4.21, Group B = 11.04 ± 4.86, Group C = 10.02 ± 4.7, Group D = 6.23 ± 4.16, p < 0.001, respectively). Other basline characteristics were similar between the four groups (all p > 0.05). Details of baseline clinical characteristics of the PCOS participants are shown in Table 1

The association between body weight and COS characteristics

Compared with lower weight group, initial Gn dosage and total dosage of Gn were significantly higher in higher weight group (Group A = 146.28 ± 32.12, Group B = 167.34 ± 38.96, Group C = 184.87 ± 52.76, Group D = 235.23 ± 63.93, p < 0.001, and Group A = 1370.27 ± 340.7, Group B = 1607.21 ± 442.52, Group C = 1826.01 ± 487.96, Group D = 2326.7 ± 894.73, p < 0.001, respectively). Notably, more patients presented HOR in lower weight groups compared to higher weight groups, with 62.16% HOR patients in Group A, 64.86% in Group B, 57.89% in Group C, and 31.82% in Group D (p = 0.037). Also, patients with lower body weight also had lower OSI (Group A = 122.67 ± 93.50, Group B = 138.80 ± 138.05, Group C = 140.60 ± 81.86, Group D = 208.98 ± 102.35, p = 0.041). Details of the COS parameters of the four weight groups were displayed in Table 2.

In our logistic regression analysis, we adopted body weight and significantly different baseline characteristics, including BMI, T, LH, and AMH. Also, we added age in our multivariate regression model. We found that increased body weight was an independent factor that was significantly associated with the increase in initial Gn dosage (OR = 1.113, 95% CI = 1.021-1.227, p = 0.016). In addition, AMH was inversely correlated with initial Gn dosage (OR = 0.856, 95% CI = 0.810-0.925, p < 0.001). Patient's age, BMI, and T level were not associated with initial Gn dosage in our analysis (Table 3).

The baseline characteristics, COS parameters, and reproductive outcomes in PCOS patients with high and normal ovarian response

There were 135 patients of HOR and 92 patients of NOR in our study. And no one expressed POR. Compared with PCOS patients with HOR, those with NOR had higher body weight (58.21 ± 9.68 vs. 55.73 ± 7.25, p = 0.039), lower AMH level (8.09 ± 4.76 vs. 12.1 ± 4.25, p < 0.001), lower LH to FSH ratio (1.31 ± 0.82 vs. 1.92 ± 1.47, p < 0.001), and less percentage of PCOM of both sides. During COS, higher initial Gn dosage (170.00±48.47 vs. 182.07±51.93, p = 0.075), higher total Gn dosage (1812.04 ± 560.82 vs. 1612.31 ± 543.45, p = 0.008) and less oocytes retrieval (9.86 ± 3.37 vs.

20.36 ± 7.57, p < 0.001) were observed in NOR patients, accompanied by higher OSI (91.32±47.65 vs. 219.89±144.90, p < 0.001). The HOR had more mature oocytes (20.36 ± 7.57 vs. 9.86 ± 3.37, p < 0.001), D3 embryos (11.21 ± 6.69 vs. 5.42 ± 3.31, p < 0.001), good-quality embryos (6.6 ± 5.12 vs. 3.6 ± 2.45, p < 0.001), blastocysts (7.35 ± 5.37 vs. 3.65 ± 2.43, p < 0.001), good-quality blastocysts (3.07 ± 2.35 vs. 1.63 ± 0.76, p < 0.001) than the NOR. There was no significant difference in the rate of oocyte maturation, embryo formation or embryos of high quality, neither with the clinical pregnancy rate after fresh ET. Moreover, HOR patients had significantly higher fresh ET cancellation rate and severe OHSS rate (84.44% vs. 19.57%, p < 0.001 and 8.88% vs. 1.09%, p = 0.017, respectively), which were more obvious than the difference of embryos. Details of the comparison of HOR and NOR PCOS patients were displayed in Table 4 and Figure 1.

The performance of body weight in predicting lowering initial Gn dosage (< 150 IU/day) in PCOS patients with NOR

All patients presented NOR received an initial Gn dosage between 100 IU and 300 IU. A ROC curve was drawn to identify the optimal cut-off value of body weight in predicting Gn dosage less than 150 IU and 225 IU (Figure 2). As to initial Gn dose of 150 IU, the AUC was 0.700 (95% CI: 0.592-0.808, p = 0.001). Body weight of 55.5 kg was selected as the optimal cut-off value with a sensitivity of 72.5% and a specificity of 63.4% (Figure 2A). The AUC was 0.854 (95% CI: 0.704-1.000, p =0.001) for initial Gn dose of 225 IU, and the cut-off value was 70.5 kg for body weight (sensitivity, 75.0%; specificity, 95.2%) (Figure 2B).

Discussion

In this retrospective cohort study, we found that increased body weight was significantly correlated to the increase of initial Gn dosage which was also associated with HOR. Compared with HOR patients, NOR patients had significantly less fresh cycle cancel rate and OHSS rate which outweighed the slightly fewer embryos. In this way, we believed that adjusting initial Gn dosage based on body weight may be beneficial to reproductive outcomes in PCOS patients. Therefore, using ROC curves, we identified 55.5 kg and 70.5 kg as the optimal cut-off values to predict the initial Gn dosage no more than 150 IU and 225 IU, respectively.

According to our results, high body weight was associated with an increased level of BMI, T, LH and AMH. We found that there was a relationship between initial Gn dose and body weight and AMH. An appropriate dosage of Gn is necessary during ovarian stimulation to improve synchronization of follicular growth and maturity of oocytes at retrieval and avoid unpredicted POR at the same time[19]. For young women with AFC>15, rFSH dose (IU per kg) was related to ovarian response, and the starting dose of rFSH adjusted for body weight had a prediction role on day 5 median follicle size and the proportion of antral follicles recruited, when adjusted by age, AFC and pre-treatment FSH level[14]. Considering the importance of body weight, we reported a correlation between starting dose of Gn and body weight, after adjusting for age, BMI, T and AMH.

Several factors have been put forward to adjust the Gn dose during COS, including ovarian response, AMH, and AFC [20]. Involving two or more factors could help improve COS results significantly. Some had individualized rFSH doses based on the consistency in r-FSH starting doses for individualized treatment (CONSORT) dosing algorithm[21]. It took basal FSH, BMI, age and AFC into consideration and resulted in an overall clinical pregnancy rate of 34.2%. Together only 2 of 161 women developed severe OHSS and the cancellation rate was 14.9%. The lowest rFSH dose group (75 IU) had a cancellation rate as much as 25% due to inadequate response. However, patients with more than 25 oocytes retrieved, history of severe OHSS, or BMI over 30 kg/m2 were excluded. One study set the optimal number of oocytes retrieval to be 9 in women younger than 40[11]. They constructed a nomogram of FSH starting dose, irrespective of the body weight, for the reason that they found an association between ovarian sensitivity and age, serum AMH and basement FSH. They also failed to include women with irregular menstrual cycle or presented PCOM. Another two

PIVET rFSH algorithms adjusted by AMH, AFC, BMI and age, were conducted to optimize the oocytes retrieval of no more than 15[9]. The researchers found that the need for elevation rFSH dose increased with the starting dose reduction. The cancellation rate of all and no more than 75 IU FSH groups were 6.2% and 8.7%, respectively. Unfortunately, the clinical pregnancy and live birth outcomes of hyper-responders were not provided.

A higher incidence of HOR in patients with relatively lower body weight was observed in our study, although they received less total Gn dose during COS. Patients with HOR may be more sensitive to Gn, which was reflected by the less OSI than the NOR, emphasizing the importance of Gn adjustment. Compared with those who showed NOR, patients with HOR, although had slightly more embryos, had about 8 times of incidence of OHSS and 4 times of fresh cycle cancel rate. Limited studies focused on the ovarian stimulation of hyper-responders. In 2018, a meta-analysis summarized the effect of Gn dose grouped by ovarian reserve tests[22]. Only two studies were included in predicted hyper-responders part (AFC>15 or AMH 15-50 pmol/l). The results showed that decreasing the dose from 150IU did not make a difference in clinical pregnancy and live birth rates, while it did reduce the risk of moderate and severe OHSS. Similar results were reported by a previous study that lowered the FSH dose in patients with AMH >32 pmol/L[23]. Our results together with these findings showed that the weakening of actual ovarian response reflected by oocytes retrieval and transferable embryos did not outweigh clinical outcomes. As the clinical outcomes would not be improved or even impaired when more than 15-20 oocytes were recovered, together with increased risk of early OHSS or thromboembolic events[24-26]. It is reasonable and vital to control the incidence of HOR. We also found that HOR women expressed relatively higher AMH, LH to FSH ratio, and PCOM, indicating these patients had more serious endocrine dysfunction.

According to ESHRE guideline recommendations, a Gn dose of 150 IU in GnRH antagonist protocol was suggested for high responders[27]. However, the pharmacokinetics and pharmacodynamics of Gn should be individualized to different patients. The excess weight affects the ovarian response to Gn[28]. Exogenous serum FSH level is inversely associated with body weight[29]. The volume of extracellular fluid is a key factor in drug distribution. Women with elevated BMI own a larger portion of fat tissue, which contributes low content of extracellular water than those without [12, 30]. In other words, for two patients with the same BMI, the one with a higher body weight owns more extracellular fluid than the other. Therefore, body weight is more predominant in determining FSH distribution than BMI[30]. A previous study found that reducing the FSH dose in predicted hyper responders with body weight > 55kg significantly decreased the OHSS occurrence but also decreased the probability of live birth[29]. On the contrary, a randomized controlled trial (RCT) found that reduction of Gn dosage significantly lowered the OHSS incidence, together with no influence on live birth rates[16]. However, women involved in this study were free from PCOS. Some researchers came up with a Low-Dose stimulation with a basement dose of 75 IU and increment/decrement of 25-50 IU according to age, AMH, BMI, and previous onset of OHSS. Patients with PCOS and the control group had comparable clinical pregnancy rates (32.2% vs. 34.4%) and moderated or severe OHSS rates (16.9% vs. 15.7%). Additionally, there was no cancellation because of unexpected poor responses [8]. One research made a cut-off value of 60 kg to decrease FSH dose from 150 IU to 112.5 IU in PCOS patients but did not explain the possible reason behind it[31]. In our study, as all patients presented HOR or NOR, we aimed to clarify the exact body weight to predict the need of lowering down initial Gn dosage from 150 IU or 300 IU, to prevent the risk of HOR. We suggested that patients with body weight below 55.5 kg required a starting dose of Gn dosage less than 150 IU, and 70.5 kg for Gn dose less than 225 IU, based on the data from NOR patients.

However, our study also has several limitations. Firstly, as a retrospective study, there might be selective bias. Therefore, we collected and compared the baseline characteristics of the enrolled participants. Secondly, the sample size of our study was relatively small, which might cause the insignificance of some findings due to limited power. Thirdly, this study was conducted in a single reproductive center which may limit the external validity of our findings.

Also, we were not able to access the pregnancy results and cumulative live birth rate due to the limited following-up time. A multicenter study with a larger sample size and a longer follow-up period is needed to provide a more convincing result.

Conclusions

In summary, our result showed a relationship between body weight and Gn starting dose in ART, which was often overlooked by previous studies. Adjusting initial Gn dosage according to body weight is of great importance for better reproductive outcomes in PCOS patients and further large scale, randomized controlled trials should be encouraged in this field.

Abbreviations

PCOS: polycystic ovarian syndrome

ART: assisted reproduction technology

IVF: in vitro fertilization

ET: embryo transfer

ICSI: intracytoplasmic sperm injection

OHSS: ovarian hyperstimulation syndrome

Gn: gonadotropin

AMH: anti-Mullerian hormone

BMI: body mass index

FSH: follicle stimulating hormone

HOR: high ovarian response

ESHRE/ASRM: European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine

COS: controlled ovarian stimulation

GnRH: gonadotropin-releasing hormone

FHA: functional hypothalamic amenorrhea

POI: premature ovarian insufficiency

T: testosterone

DHEAS: dehydroepiandrosterone sulfate

AND: androstadienone

SHBG: sex hormone-binding globulin

LH: luteinizing hormone

AFC: antral follicle count

hCG: human chorionic gonadotropin

E2: estradiol

P: progesterone

OSI: ovarian sensitivity index

PN: pronucleus

POR: poor ovarian response

NOR: normal ovarian response

TVS: transvaginal ultrasound

ANOVA: analysis of variance

OR: odds ratio

CI: confidence interval

ROC: receiver operating characteristic

AUC: area under curve

CONSORT: consistency in r-FSH starting doses for individualized treatment

RCT: randomized controlled trial

Declarations

Ethical Approval and Consent to participate

The Ethical Review Board of West China Second University Hospital, Sichuan University approved the study and waved the need for written informed consent (Approval No. 2021-033).

Consent for publication

All authors consent.

Availability of supporting data

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

XZ and LQ designed the study. RZ had full access to all the data in the study. HC performed the statistical analyses. RZ, HC, XZ and LQ contributed with the clinical interpretation of the results. RZ and HC drafted the manuscript. All authors read and approved the final version of the article.

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Tables

Table 1 Baseline characteristics of PCOS patients in four body weight groups (n=227).

Characteristics		Weight 40~50kg Group (n=37)	Weight 50~60 kg Group (n=111)	Weight 60~70 kg Group (n=57)	Weight ≥70 kg Group (n=22)	P
Age (years)		28.57±2.54	29.73±3.49	29±3.45	28.91±4.14	0.246
Type of infertility	Primary	78.38%(29/37)	65.77%(73/111)	68.42%(39/57)	54.55%(12/22)	0.195
	Secondary	16.22%(6/37)	27.03%(30/111)	29.82%(17/57)	45.45%(10/22)	
	Other	5.41%(2/37)	7.21%(8/111)	01.75%(1/57)	0%(0/22)	
Oligo/hypomenorrhea		97.30%(36/37)	87.39%(97/111)	96.49%(55/57)	86.36%(19/22)	0.085
BMI (kg/m2)		18.6±1.49	21.47±1.52 [ab]	24.94±1.59 [cd]	28.33±2.09 [ef]	<0.001*
T (ng/ml)		0.47±0.18	0.44±0.17	0.49±0.22 [d]	0.83±1.33 [ef]	0.003*
DHEAS (ug/dl)		188.44±52.76	210.01±87.2	245.28±107.78	288.25±210.31	0.051
AND (ng/ml)		3.34±1.22	3.38±1.24	3.47±1.15	4.19±2.56	0.328
SHBG (nmol/L)		62.63±21.38	49.13±37.29	53.72±62.4	29.25±18.35	0.198
LH/FSH		2.09±1.16	1.65±1.04	1.60±1.79	1.26±0.82	0.091
AFC≥24		78.38%(29/37)	73.87%(82/111)	82.46%(47/57)	77.27%(17/22)	0.656
AMH (ng/ml)		11.99±4.21	11.04±4.86	10.02±4.7 [cd]	6.23±4.16 [ef]	<0.001*

BMI, body mass index; T, testosterone; DHEAS, dehydroepiandrosterone sulfate; AND, androstadienone; SHBG, sex hormone-binding globulin; FAI, free androgen index; FSH, follicle-stimulating hormone; LH, luteinizing hormone; AFC, antral follicle count; AMH, Anti-Mullerian hormone. *, P values < 0.05; [a], p<0.05 between Group A and Group B; [b], p<0.05 between Group B and Group C; [c], p<0.05 between Group A and Group C; [d], p<0.05 between Group C and Group D; [e], p<0.05 between Group A and Group D; [f], p<0.05 between Group B and Group D.

Table 2 Controlled ovarian stimulation characteristics of PCOS patients four body weight groups (n=227).

Characteristics		Weight 40~50kg Group A (n=37)	Weight 50~60 kg Group B (n=111)	Weight 60~70 kg Group C (n=57)	Weight ≥70 kg Group D (n=22)	P
Initial Gn dosage (IU/day)		146.28±32.12	167.34±38.96 [ab]	184.87±52.76 [cd]	235.23±63.93 [ef]	<0.001*
Stimulation time (days)		9.49±1.46	9.86±1.39	10.23±1.63	10.14±1.7	0.108
Total dosage of Gn (IU)		1370.27±340.7	1607.21±442.52 [ab]	1826.01±487.96 [cd]	2326.7±894.73 [ef]	<0.001*
Number of oocytes with diameter ≥14mm on hCG day		11.05±3.37	10.31±3.91	9.68±2.77	8.45±2.32	0.030*
E2 on hCG day (pg/ml)		6224±3236.26	5660.68±3194.1	4878.6±3012.36	2996.21±1365.46	<0.001*
P on hCG day (ng/ml)		1.17±0.5	1.13±0.56	1.01±0.51	1.16±1.84	0.689
LH on hCG day (IU/L)		2.53±2.51	2.8±2.74	2.76±2.14	2.47±1.36	0.903
Endometrial thickness on hCG day (mm)		5.09±0.82	5.06±0.95	5.01±0.9	4.93±0.84	0.912
Ovarian response	High	62.16%(23/37)	64.86%(72/111)	57.89%(33/57) [d]	31.82%(7/22) [ef]	0.037*
	Normal	37.84%(14/37)	35.14%(39/111)	42.11%(24/57)	68.18%(15/22)	
OSI (IU)		122.67±93.50	138.80±138.05	140.60±81.86 [d]	208.98±102.35 [ef]	0.041*

Gn, gonadotrophin; E2, estradiol; P, progesterone; LH, luteinizing hormone; OSI, ovarian sensitivity index. *, P values < 0.05; [a], p<0.05 between Group A and Group B; [b], p<0.05 between Group B and Group C; [c], p<0.05 between Group A and Group C; [d], p<0.05 between Group C and Group D; [e], p<0.05 between Group A and Group D; [f], p<0.05 between Group B and Group D.

Table 3 Logistic regression analysis of initial Gn dosage

	OR	SE	P	95%CI
Age	1.007	0.045	0.874	0.922-1.100
Weight	1.113	0.047	0.016	1.021-1.227
BMI	0.942	0.118	0.621	0.749-1.189
T	0.967	0.421	0.938	0.424-2.211
LH	0.999	1.016	0.943	0.969-1.034
AMH	0.855	0.034	<0.001	0.809-0.926

BMI, body mass index; T, testosterone; AMH, Anti-Mullerian hormone; OR, odds ratio; SE, standard error; CI, confidential interval.

Table 4 Comparison of characteristics in PCOS patients with high ovarian response and normal ovarian response

Characteristics	HOR group (n=135)	NOR group (n=92)	P
Age (years)	29.34±3.44	29.18±3.41	0.737
Oligo/hypomenorrhea (%)	92.59%(125/135)	89.13%(82/92)	0.366
Height (cm)	158.56±4.61	158.86±4.73	0.639
Weight (kg)	55.73±7.25	58.21±9.68	0.039*
BMI (kg/m2)	22.03±3.36	22.86±4.42	0.133
T (ng/ml)	0.49±0.26	0.51±0.65	0.758
DHEAS (ug/ml)	226.26±122.12	207.54±97.39	0.398
AND (ng/ml)	3.62±1.46	3.18±1.41	0.118
SHBG (nmol/l)	50.01±35.65	49.92±48.24	0.993
AMH (ng/ml)	12.1±4.25	8.09±4.76	<0.001*
LH/FSH	1.92±1.47	1.31±0.82	<0.001*
AFC≥24	83.70%%(113/135)	67.39%(62/92)	0.004*
Initial Gn dosage (IU/day)	170.00±48.47	182.07±51.93	0.075
Stimulation time (days)	9.84±1.43	10.03±1.61	0.357
Total Gn dosage (IU)	1612.31±543.45	1812.04±560.82	0.008*
Number of oocytes retrived	20.36±7.57	9.86±3.37	<0.001*
OSI (IU)	91.32±47.65	219.89±144.90	<0.001*
Normal fertilization rate	62.94%(1807/2871)	61.86(605/978)	0.547
Number of D3 embryos	11.21±6.69	5.42±3.31	<0.001*
Number of good-quality D3 embryos	6.6±5.12	3.6±2.45	<0.001*
Number of blastocysts	7.35±5.37	3.65±2.43	<0.001*
Number of good-quality blastocysts	3.07±2.35	1.63±0.76	<0.001*
Fresh ET cancellation rate	84.44%(114/135)	19.57%(18/92)	<0.001*
Clinical Pregnancy rate after fresh ET	59.26%(80/135)	52.17%(48/92)	0.291
Severe OHSS rate	8.88%(12/135)	1.09%(1/92)	0.017*

HOR, high ovarian response; NOR, normal ovarian response; OSI, ovarian sensitivity index; ET, embryo transfer; OHSS, ovarian hyperstimulation syndrome. *, P values < 0.05.

Figures

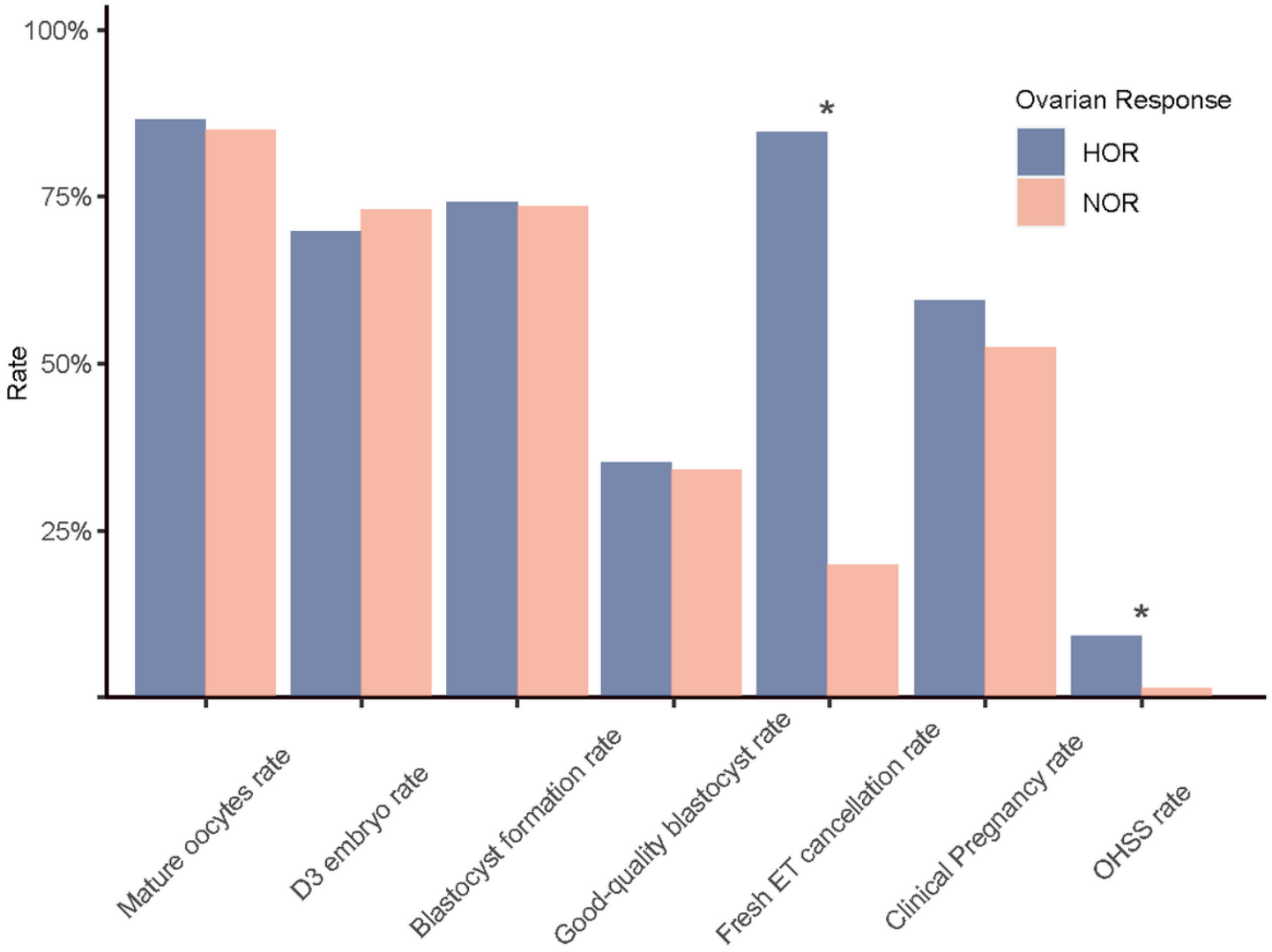

Figure 1

Barplots of reproductive outcomes in PCOS patients with high ovarian response and normal ovarian response. HOR, high ovarian response; NOR, normal ovarian response. *, P values < 0.05.

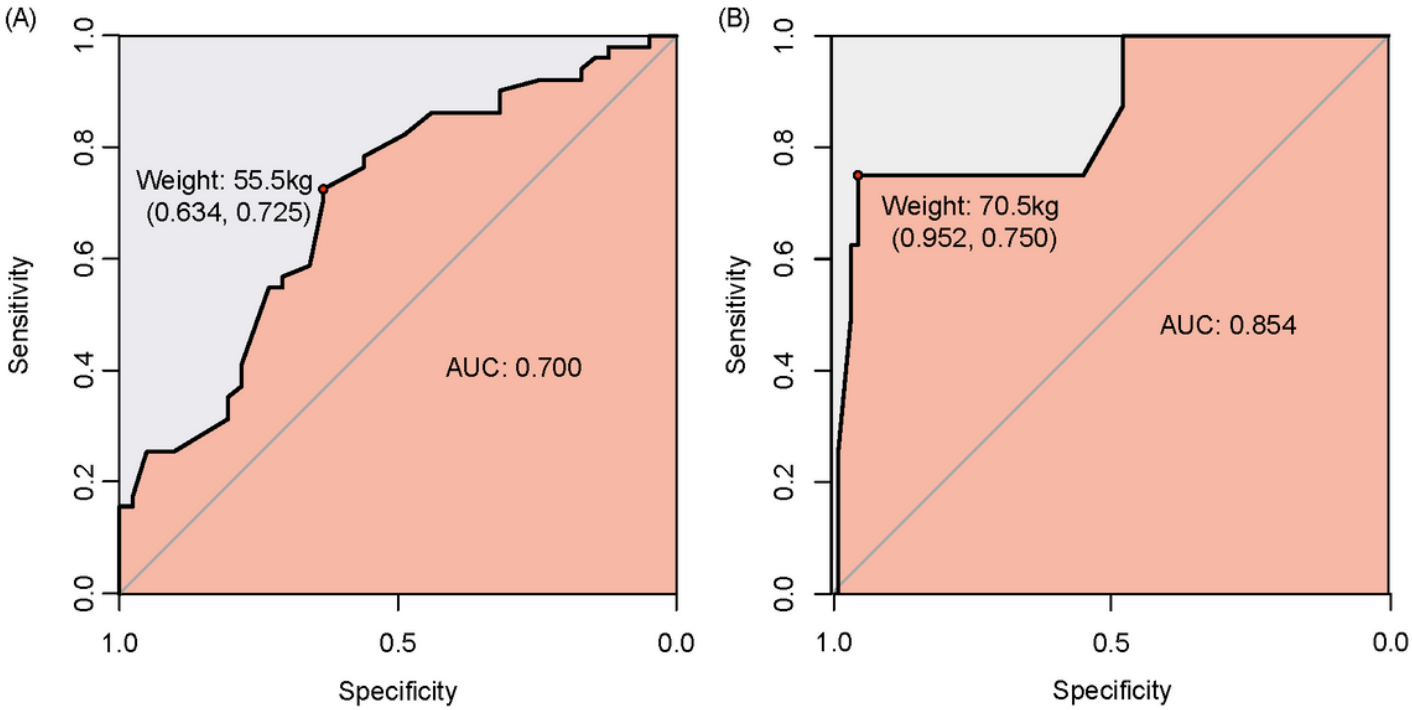

Figure 2

Receiver operating characteristic curves of body weight in predicting initial Gn dosage set up in PCOS patients with normal ovarian response. A, body weight in predicting initial Gn dosage higher than 150 IU/day in PCOS patients with normal ovarian response; B, body weight in predicting initial Gn dosage higher than 225 IU/day in PCOS patients with normal ovarian response. AUC, area under curve.