Al-Kindy College Medical Journal (KCMJ)

Research Article

Effectiveness and Safety of Highly Purified Human Menopausal Gonadotropin in Hyper Responder Iraqi Females Undergoing Intracytoplasmic Sperm Injection

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Article history:
Received 18 August 2024
Accepted 6 December 2024
Available online 1 April 2025

https://doi.org/10.47723/kzzes928

Keywords: recombinant follicle-stimulating hormone; highly purified human menopausal gonadotrophin; ovarian hyper stimulation syndrome; Pregnancy rate

ABSTRACT

***Background*:** The response to ovarian stimulation in females is heterogeneous, so treatment individualization offers both safety and efficacy. The use of highly purified human menopausal gonadotrophin (HP-hMG) during controlled ovarian stimulation is widely accepted nowadays but with absence of evidence demonstrating the advantages of this gonadotrophin.
Objective: To evaluate the efficacy and safety of highly purified human menopausal gonadotrophin vs. recombinant follicle-stimulating hormone (rFSH) in controlled ovarian hyperstimulation for hyper responder females undergoing intracytoplasmic sperm injection.
***Subjects and methods*:** Eighty- one sub-fertile females who were admitted to the infertility center of High Institute for Infertility Diagnosis and Assisted Reproductive Technologies/ Al-Nahrain university, during the period from January 2020 to December 2023 were included in the present study. GnRH antagonist down regulation was used for all participants. According to gonadotrophin type used for ovarian hyperstimulation females were divided into 2 groups: group who was stimulated with r- FSH and the other group who were stimulated with HP-hMG.
***Results*:** Females who were stimulated by r-FSH showed insignificantly higher total number of retrieved oocytes, mature oocytes and lower immature oocytes yield. In addition, they had a significantly higher pregnancy rate (29 % vs 0%), and higher OHSS rate (26.08% vs 16.66%), compared to those stimulated by HP-hMG.
***Conclusion*:** In hyper responders; highly purified human menopausal gonadotrophin provides lower efficacy but higher safety than recombinant follicle-stimulating hormone in terms of oocyte yield, pregnancy rate and OHSS development

Introduction

Assisted reproduction includes all the procedures used for fertilization, which is not achieved through sexual intercourse (1). GnRH antagonist protocols may be the most prevalent protocols designed to inhibit the LH surge in Intracytoplasmic sperm injection (ICSI) cycles, the leading follicular size was depended as criterion to start the inhibition in addition to endometrial thickness at day of antagonist correlates significantly with pregnancy rates and it can be taken as criteria to initiate GnRH antagonist (2)

Patients undergoing assisted reproductive technologies (ART) usually exhibit variable responses to exogenous gonadotropin during controlled ovarian stimulation (COS)(3). Personalization of gonadotropin (Gn) treatment is usually needed to get better response to treatment in form of efficacy, safety, and cycle efficiency. Development of newer treatments' technologies can give us an opportunity to achieve such personalization by tailoring gonadotropin type and dose according to ovarian response (4). It was found that serum and follicular fluid kisspeptin are positively correlated with the cumulative recombinant FSH dose used by infertile PCOS women undergoing ICSI, addressing the possible role of kisspeptin in improving the pregnancy rate in these patients with a lower incidence of ovarian hyperstimulation syndrome (5).The use of GnRH agonist to trigger final maturation of oocytes and embryos freeze all is considered the only proved measure that eliminates the incidence of ovarian hyper stimulation syndrome (OHSS) when the patients produce a high number of oocytes (6). However, undesirable outcome is not uncommon; increase in cost, decrease time to pregnancy, adverse effects of cryopreservation on embryos' quality, decrease endometrial receptivity and increase the need for intensive luteal phase support (7).

Antral follicle count (AFC) by trans-vaginal ultrasound and serum level of antimüllerian hormone (AMH) both have been shown to be best predictors of ovarian response (8,9). Due to lack of AFC methodological standardization, AMH considered the preferable biomarker to predict the treatment response, particularly in the context of multi-center clinical trials (10). Serum AMH level can be successfully guided the Gn dosing in COS. Serum AMH measurements have been successfully used to predict likely high responders (11).

Current strategies for such patients are usually reactive and result in delaying time to pregnancy to mitigate the risk of OHSS instead of proactive benefit (12). Thus, it is very important, prior to the start of stimulation, to identify females who are at risk for hyper response, and to develop new treatment approaches to improve the outcome in such group of females (3). Females with AMH ≥ 4.45ng/ml and/or AFC ≥ 12 at the 2nd / 3rd of menstrual cycle and serum E2 level before the day of ovulation trigger ≥4459 pg/ml are considered as predicted or expected hyper responder (13). There are different types of gonadotropins that can be introduced for COS, best treatment option is not yet known. r-FSH has been widely and successfully used for ovarian stimulation in infertile women (14) In addition to r-FSH, a trend toward the importance of LH activity during COS in the GnRH antagonist/agonist down-regulated ICSI cycles (15), LH activity can be administered in different forms; one of these is highly purified (HP)-hMG (75 IU FSH: 75 IU LH) with a 70% purity. HP-hMG provides FSH and LH activity mainly in the form of hCG (16,17).

LH activity in form of HP-hMG when administered early during stimulation cycle induces high endogenous androgen level which stimulates the up-regulation of FSH receptors during the early stage of follicular development, decreases granulosa cells proliferation, recruitments of more selective follicle, modulates the number of follicles and thus provides better safety with a lower risk of high response than r-FSH (18). Both protocols have comparable effects on ICSI outcome, so, further studies are recommended (3).

Subjects and Methods

A retrospective study that included 81 sub-fertile females who seek ICSI treatment at Al-Kafeel IVF center/Holly Karbala/Iraq and infertility center of High Institute for Infertility Diagnosis and Assisted Reproductive Technologies/ Al- Nahrain university, during the period from January 2020 to December 2023. Their age ranged 21-45 years old and their body mass index 18-30 kg/m2. All are considered to be predicted hyper responders whom their AMH ≥ 5 ng/ml or their cycle day 2 AFC ≥12. They are ovulatory who seek ICSI either due to tubal blockage or male factor. They were evaluated clinically, blood was drawn at the 2nd day of cycle and hormonal profile was measured (E2, LH, FSH, AMH, prolactin). TVUS for AFC, endometrial thickness and any endometrial and ovarian pathology. They were down regulated using GnRH antagonist protocol (Cetrotide 0.25 mg S.C, Serona) administered at a fixed day; day 6 of stimulation cycle. The stimulation was done either with r-FSH (Follitrope 75 IU *2, Merk, S.C) or HP-hMG (Menopur, Merk 75 IU*2, S.C) starting from the 2nd day of menstrual cycle with dose adjusted accordingly. After a treatment period of 10 to 14 days, oocyte pick up was done under general anesthesia and TVUS when a good number of follicles reach a maturation of size more than 16-18 mm which was done 36 hours after triggering by hCG (Pregnyl 5000 IU*2, I.M, Organon). At the same time a fresh semen ejaculate was taken from the husband and ICSI was performed. Luteal phase progesterone (cyclogest sup. Of 400 mg*2) and progesterone IM injection every two days started at the evening of oocyte retrieval day. Microscopic assessment of oocytes and embryos was done and a comparison between the two groups (group 1: r-FSH was used, n=69 and group 2 : HP-hMG was used, n=12) was estimated. Fresh embryo transfer was done under TVUS using embryo transfer catheter when at least 2 good quality embryos (day 3 or 8 cell stage) were transferred, 14 days later, pregnancy was assessed by measuring serum beta-HCG in the serum. A formal consent was taken from the couples and ethical approval committee at Kerbala university/college of medicine (No. 10, at 15-5-2023). Anovulatory (those with polycystic ovary syndrome), females with BMI ≥ 30 kg/m2, low AFC ≤ 12, AMH ≤ 5 ng/ml, thyroid disorders, severe endometriosis and whom their husband had sever impairment in semen quality or testicular extracted frozen semen were excluded from the study.

Results

Table 1 shows the demographic data of the studied groups; their mean age is 27.23±4.08 years and mean BMI of 28.39±4.15 kg/m2. There was significant difference regarding the BMI between both groups being higher in the group who were stimulated with HP-hMG, p-value of 0.002. Regarding the type of infertility, there was significant difference between both groups at a p-value of 0.0001.

The ovarian response to the stimulation protocols is illustrated in table 2. Despite of being insignificant, women who were stimulated with HP-hMG produced lower number of oocytes, mature oocytes, embryos and good quality embryos than those who stimulated with r-FSH.

Table 1: Comparison of age, BMI, duration and type of infertility in the studied groups.

Studied variable	r-FSH Mean±SD N=69	HP-hMG Mean±SD N=12	P-value
Age(years)	27.23±4.08	29.00±3.411	0.16
BMI(kg/m2)	25.39±4.15	28.39±4.15	0.002*
Duration of sub-fertility(years)	6.88±3.089	6.60±3.56	0.79
Type of sub-fertility			
Primary	47	10	0.0001**
Secondary	22	2	
Total	69	12	81

Table 2: comparison of ovarian response to stimulation protocols between studied groups.

Studied variable	r-FSH Mean±SD N=69	HP-Hmg Mean±SD N=12	P-value
Total number of oocytes	14.19±7.87	10.50±8.52	0.14
Total number of mature oocytes	12.13±7.37	8.50±8.71	0.13
Total number of immature oocytes	2.32±3.037	2.00±1.34	0.71
Total number of embryos	7.23±4.10	6.66±6.75	0.69
Total number of good quality embryos	7.04±4.06	6.50±6.40	0.69
Total number of bad quality embryos	0.19±0.50	0.17±0.38	0.85

Table3: Comparison of Endometrial thickness (ET) and serum estradiol level (E2) at the day of trigger, pregnancy rate and OHSS development rate.

Studied variable	r-FSH Mean±SD N=69	HP-hMG Mean±SD N=12	P-value
ET (mm)	10.15±2.55	9.66±2.309	0.53
E2	4118.75±12399.94	1088.04±547.98	0.05
Pregnancy rate			
Pregnant	18(29%)	0(0%)	0.02
Not pregnant	44	10	
Total	62	10	
OHSS			
Yes	18 (26.08%)	2(16.66%)	0.0001
No	51	10	
Total	69	12	

Table 3 shows endometrial thickness (ET) and serum estrogen level (E2) at the day of oocyte maturation trigger, pregnancy rate and OHSS development rate. There was significant statistical variance between both groups regarding serum E2 level, pregnancy rate and OHSS development rate. Pregnancy rate was higher in females who stimulated by r-FSH 29% versus 0% in the HP-hMG group, while OHSS development rate was significantly less in the HP-hMG 16.66% versus 26.08 in the r-FSH groups at a p-value of 0.02 and 0.0001 respectively.

Discussion

Two types of gonadotropins are used to stimulate the ovaries to produce more oocytes during COS and multiple studies were done to compare between them suggesting a comparable outcome (19,20). Studies reported that hMG-stimulated females, in a comparison with r-FSH, produce lower number of retrieved oocytes with best quality oocytes and embryos (21,22). This may be related their BMI being higher in the study group and as it is known that obesity reduces fertility; females with a body mass index (BMI)≥ 30 kg/m2 had a 2.7-fold higher risk of infertility (23,24). As predicted hyper responder females produce high number of oocytes which are the major responsible factor for OHSS development and its complications (12). So, researchers tried to study the hMG effectiveness in this group of females in reducing this risk. The current study showed that hMG stimulated females produced insignificantly lower number of oocytes, mature oocytes and a comparable number of embryos and good quality embryos and significantly lower pregnancy and OHSS development rate. These results were similar to what was suggested by Witz et al., who concluded that hMG when used in hyper responder provided comparable efficacy to r-FSH with fewer adverse events, including pregnancy loss (3). Ana et al tried to confirm what was reached by Witz et al and their results were same and females stimulated by hMG had lower OHSS development rate (25). Similar results are reached by several studies and it all suggested that using HP-hMG during COS/ICSI may have better safety and same efficacy with the exception of pregnancy rate which need to be evaluated more to reach a final decision (26).

Study limitations: larger sample size is needed with using of different gonadotrophin types

Conclusion

r-FSH use for ovulation induction in hyper responders provides higher oocyte yields, with higher maturity rate, good quality embryos and higher pregnancy rate but with higher incidence of OHSS

Acknowledgments

Great thanks to all members of Al-Kafeel IVF center and High Institute for Infertility Diagnosis and Assisted Reproductive Technologies/ Al- Nahrain university for their help to complete the study

Funding

This research did not receive any specific fund.

Conflict of Interest

Authors declare no conflict of interest.

Data availability

Data are available upon reasonable request.

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To cite this article:
Abbood MS, Falah Hassan M, Badai Nashtar S. Effectiveness and Safety of Highly Purified Human Menopausal Gonadotropin in Hyper Responder Iraqi Females Undergoing Intracytoplasmic Sperm Injection. Al-Kindy Col. Med. J. 2025;21(1):53-57.
https://doi.org/10.47723/kzzes928