

The Impact of Gonadotropin Type on Controlled Ovarian Stimulation and Intrauterine Insemination Cycle Outcomes

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ABSTRACT

Background: Intrauterine insemination (IUI) combined with controlled ovarian stimulation (COS) results in higher pregnancy rates. However, there is still no consensus on the optimal COS protocol. **Aims:** In the present study, we aimed to analyse the effects of COS protocols with different gonadotropin types on IUI outcomes. **Study Setting and Design:** This was a retrospective cohort study conducted at the infertility clinic of a University hospital, including 237 COS + IUI cycles. **Materials and Methods:** Eligible cycles were divided into three groups according to the type of gonadotropin used for COS; cycles with recombinant follicle-stimulating hormone (rFSH) (group 1, $n = 36$), highly purified FSH (HP-FSH) (group 2, $n = 178$) and highly purified menotropin (HP-hMG) (group 3, $n = 23$). Clinical pregnancy rate (CPR) and live birth rate (LBR) per cycle were compared between groups. **Statistical Analysis Used:** The Mann–Whitney U test and Kruskal–Wallis test were used to compare numerical variables. Dunn test was used for multiple comparisons. **Results:** The duration of stimulation and total gonadotropin dose were similar between the three groups ($P > 0.05$). The CPR was 16.7% in rFSH group, 9.6% in HP-FSH group and 13.0% in HP-hMG group. The LBR was 16.7% in rFSH group, 8.4% in HP-FSH group and 13.0% in HP-hMG group. Both CPR and LBR were comparable in all three groups ($P > 0.05$). **Conclusions:** Ovarian stimulation with rFSH, HP-FSH and HP-hMG show similar COS characteristics. Furthermore, these three gonadotropin protocols for COS + IUI yielded comparable CPR and LBR. These findings suggest that all three gonadotropin types (rFSH, HP-FSH, HP-hMG) are similarly effective in COS + IUI cycles.

KEYWORDS: Artificial insemination, assisted reproductive techniques, follicle-stimulating hormone, gonadotropin, infertility, menotropin, ovarian stimulation, urofollitropin

INTRODUCTION

Infertility is defined as the failure to achieve a pregnancy after 12 months or more of regular unprotected sexual intercourse. It is a global health problem affecting about 8%–12% of couples of reproductive age.^[1] Intrauterine insemination (IUI) is a commonly used treatment approach for infertile patients. It is simple, safe, inexpensive and less invasive than assisted reproductive technology (ART) treatments.^[2] On the other hand, IUI has a lower success rate than

ART methods.^[3] Extensive research has shown that various factors affect IUI success, such as female age, sperm parameters, infertility duration and aetiology, number of treatment cycles and number of pre-ovulatory follicles.^[4-6]

An important factor affecting the IUI success is the combination of IUI with controlled ovarian stimulation (COS). Studies have shown that IUI in

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a stimulated cycle results in higher pregnancy rates than in a natural cycle.^[7-9] However, there is still no consensus on the optimal COS protocol for IUI.^[10] Previous studies showed better reproductive outcomes after ovarian stimulation with gonadotropins compared to other ovarian stimulating agents.^[11-14] Recombinant follicle-stimulating hormone (rFSH), human menopausal gonadotropin (hMG) and highly purified urinary FSH (HP-FSH) are the main gonadotropins used for COS + IUI cycles.^[10] Although many studies investigated the effect of COS with different gonadotropin preparations on ART success, the number of studies evaluating the effect of these preparations on IUI success is much less. Studies on gonadotropins used for COS + IUI cycles are generally in the form of pairwise comparisons.^[15-19] A limited number of studies compared the three main gonadotropins used, namely rFSH, HP-FSH and hMG.^[14,19-21] Multiple comparative studies with gonadotropins will help determine the optimal protocol for COS + IUI cycles.

In the present study, we aimed to analyse the effects of COS protocols performed with different gonadotropin types on IUI outcomes.

SUBJECTS AND METHODS

Ethics

Ethical approval for this study was obtained from the Institutional Review Board of Kocaeli University Faculty of Medicine, Kocaeli, Turkey (approval number: KU GOKAEK-2021/12.04, date: June 18, 2021). Written informed consent was obtained from all patients. The procedures followed were in accordance with Helsinki Declaration of 1975, as revised in 2013.

Study design

This was a retrospective cohort study including 237 patients undergoing COS + IUI at ART Center of Kocaeli University Faculty of Medicine between January 2019 and December 2019.

Patients with the inability to conceive after 12 months or more of unprotected sexual intercourse were considered infertile and further evaluated. The routine infertility work-up of the female patient included transvaginal ultrasonography, hysterosalpingography, anti-Mullerian hormone (AMH), basal FSH and estradiol levels and documentation of ovulation through mid-luteal progesterone level. The infertility assessment of the male partner included an andrological examination and sperm analysis. The sperm parameters were evaluated according to the World Health Organization (WHO) 2010 criteria for semen analysis.^[22] The inclusion criteria for the study were as follows: female age between 20 and 44 years,

first or second COS + IUI cycle, at least one patent tube at HSG, ovarian stimulation performed solely with one of the three gonadotropins; rFSH (Gonal-F®, Merck Serono, Aubonne, Switzerland) or HP-FSH (Fostimon®, IBSA, Italy) or highly purified HMG (HP-hMG) (Menopur®; Ferring, Saint-Prex, Switzerland). Cycles with letrozole or clomiphene citrate use, third or higher-order cycles of the patients, cycles with incomplete or absent COS records were excluded from the study as well as cycles of patients with hypogonadotropic hypogonadism. Unexplained infertility (UEI) was diagnosed in case of normal sperm parameters according to WHO 2010 criteria^[22] and the absence of a female factor. Anovulation was diagnosed when mid-luteal progesterone was <3 ng/ml. Mild oligozoospermia was diagnosed when the sperm concentration was between 10×10^6 and 15×10^6 sperm/ml.

A total of 470 COS + IUI cycles were performed between January 2019 and December 2019 at our ART centre. Of these cycles, 237 cycles were eligible. Eligible cycles were divided into three groups according to the type of gonadotropin used for COS; cycles with rFSH (group 1, $n = 36$), HP-FSH (group 2, $n = 178$) and HP-hMG (group 3, $n = 23$). Clinical pregnancy rate (CPR) and live birth rate (LBR) per cycle were compared between groups.

Demographic and clinical characteristics including age, male age, body mass index (BMI), infertility diagnosis and duration, type of infertility (primary vs. secondary), cigarette smoking, number of previous IUI cycles, type and total dose of gonadotropin used, cycle duration, endometrial thickness and number of follicles >15 mm on human chorionic gonadotropin (hCG) day and laboratory findings including basal FSH, AMH, semen analysis of the sample used for IUI were collected from hospital records and compared between groups.

Controlled ovarian stimulation

On cycle day 2, transvaginal ultrasound was performed to evaluate endometrial thickness and ovaries. Patients were administered daily doses of rFSH or HP-FSH or HP-hMG depending on the clinician's choice. According to our institutional IUI protocol, the starting dose was 75 IU/day for HP-FSH and HP-hMG and 37.5-75 IU/day for rFSH. Follicular development was assessed 5 days after the initiation of ovarian stimulation and 2-3 days thereafter by transvaginal ultrasonography. The dose was adjusted according to the ovarian response, and the maximum gonadotropin dose administered was 150 IU per day. When 1 or 2 follicles reached a diameter ≥ 17 mm, ovulation was triggered with 250 μ g recombinant hCG (Ovitrelle®, Merck-Serono, Italy). IUI was performed either 24 or 36 h after hCG injection.

Cycles with three or more follicles ≥ 15 mm were cancelled because IUI is not allowed in Turkey when more than two pre-ovulatory follicles develop. These patients were also advised to abstain from sexual intercourse to avoid naturally conceived multiple pregnancies.

Intrauterine insemination

Semen samples were obtained by masturbation on IUI day after 3-5 days of sexual abstinence. Semen samples were analysed according to WHO 2010 criteria for semen analysis^[22] and prepared for insemination using the swim-up technique. The seminal plasma was divided into aliquots of 1 ml and overlaid by 1 ml of culture medium (Sperm Washing Medium, Fujifilm, Irvine Scientific, CA, USA). After incubation for 45–60 min at 37°C, the overlying portion was aspirated and used for insemination.

All IUI procedures were performed under transabdominal ultrasound guidance. The patient was positioned in the lithotomy position and a speculum was placed to visualise the cervix. An insemination catheter (Technocath, Istanbul, Turkey) was introduced through the internal os, and the tip of the catheter was placed approximately 1-2 cm from the uterine fundus. The insemination was performed, and the catheter was withdrawn. Patients had 10 minutes of bed rest after the insemination. The luteal phase was supported by vaginal micronized progesterone capsule (Progestan 200 mg soft capsule, Kocak Farma, Turkey) three times daily starting from the day after insemination.

Serum beta hCG test was performed 14 days after IUI. A positive beta hCG test (≥ 20 IU) was considered as a biochemical pregnancy. The presence of a gestational sac at the 7th gestational week was defined as a clinical pregnancy. Miscarriage is defined as a pregnancy loss either after a positive beta hCG test or after ultrasonographic detection of a gestational sac.

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistical Package version 20.0 (IBM Corp., Armonk, NY, USA). Kolmogorov–Smirnov and Shapiro–Wilk’s tests were used to determine whether the data is normally distributed. The continuous variables were expressed as mean \pm standard deviation (SD), or median (25th–75th percentile). Categorical variables were expressed as counts (percentages). Chi-square tests were used to compare categorical variables. Comparisons of numeric variables between groups were carried out using the Mann–Whitney U test and Kruskal–Wallis test since the normality assumption did not hold. Dunn test was used for the multiple comparisons. Sample size

calculation was not performed. All statistical analyses were carried out with 5% significance and a two-sided $P < 0.05$ was considered as statistically significant.

RESULTS

Demographic and clinical characteristics

The baseline characteristics of the patients are presented in Table 1. The mean female age was 29.4 ± 4.3 years. The mean infertility duration was 3.4 ± 2.2 years. Only 4% of the patients had secondary infertility. Of 237 cycles, 62% was a first IUI cycle. Regarding infertility aetiology, 56% of the patients had UEI, 40% had anovulation, 2% had endometriosis and 2% had mild oligozoospermia. The biochemical pregnancy rate was 14%. The CPR and LBR per cycle were 11% and 10%, respectively.

When cycles were grouped according to the gonadotropin type used for COS, there were no significant differences between groups regarding female and male age, BMI, infertility duration, number of previous trials, smoking status and basal AMH level ($P > 0.05$) [Table 2]. There was a statistically significant difference regarding basal FSH level between groups ($P = 0.007$). *Post hoc* analysis showed that the median basal FSH level was significantly higher in the HP-hMG group compared to HP-FSH group (8.8 [7.6–11.4] vs. 6.8 [5.7–8.2] respectively, $P = 0.005$). The median FSH level was comparable amongst other groups. Semen characteristics including sperm concentration, progressive motility, total progressive motile sperm count (TPMS) were also similar between groups ($P > 0.05$). In regard to infertility aetiology, all 4 cycles with mild oligozoospermia and 2 of 4 cycles with endometriosis were performed using HP-FSH so only cycles with UEI and anovulation were compared between groups. All three groups

Table 1: Baseline characteristics of the study population

Characteristics*	Study population (n=237)
Female age (year)	29.46 \pm 4.3
Male age (year)	33.11 \pm 4.8
Duration of infertility (year)	3.49 \pm 2.2
Infertility aetiology	
Anovulation	95 (40.1)
Unexplained infertility	134 (56.5)
Endometriosis	4 (1.7)
Mild oligozoospermia	4 (1.7)
Infertility type	
Primary	228 (96.2)
Secondary	9 (3.8)
Biochemical pregnancy rate	32 (13.5)
Clinical pregnancy rate	26 (11.0)
Live birth rate	24 (10.1)

*Data are presented as mean \pm SD or n (%). SD=Standard deviation

had a similar distribution of cycles with UEI and anovulation ($P = 0.097$).

Controlled ovarian stimulation outcomes

Table 3 shows the comparison between the three groups regarding COS outcomes. The duration of stimulation and the total gonadotropin dose used were similar between the three groups ($P = 0.085$ and $P = 0.674$, respectively). Furthermore, endometrial thickness and the number of follicles above 15 mm on the day of hCG were also similar in all groups ($P > 0.05$); 47% of rFSH

cycles, 49% of HP-FSH cycles, 26% of HP-hMG cycles had two follicles above 15 mm.

The CPR was 17% in rFSH group, 10% in HP-FSH group, and 13% in HP-hMG group. The LBR was 17% in rFSH group, 8% in HP-FSH group and 13% in HP-hMG group. Although CPR and LBR were higher in rFSH group, these findings did not reach statistical significance. Both CPR and LBR were comparable in all three groups ($P = 0.435$ and $P = 0.290$, respectively). The miscarriage rate was 14% in rFSH group, 40% in

Table 2: Baseline characteristics of the patients

Characteristics*	rFSH group (n=36)	HP-hMG group (n=23)	HP-FSH group (n=178)	P
Female age (year)	29.6 (27-33)	31.0 (26.0-34.0)	29.0 (26.0-32.0)	0.320
Male age (year)	33.0 (30.0-38.75)	33.0 (30.0-38.0)	32.0 (30.0-35.0)	0.258
BMI (kg/m ²)	23.4 (20.5-26.3)	26.3 (24.5-29.8)	23.8 (21.4-27.1)	0.165
Smoking status, n (%)				
Smoking	6 (20.7)	4 (81.0)	23 (15.0)	0.762
Non-smoking	23 (79.3)	17 (19.0)	130 (85.0)	
Duration of infertility (year)	3.0 (1.5-4.0)	3.0 (2.0-5.0)	3.0 (2.0-4.0)	0.483
Infertility aetiology, n (%)				
Anovulation	13 (38.2)	5 (21.7)	77 (44.8)	0.097
Unexplained infertility	21 (61.8)	18 (78.3)	95 (55.2)	
IUI attempts, n (%)				
First attempt	20 (55.6)	16 (69.6)	110 (61.8)	0.569
Second attempt	16 (44.4)	7 (30.4)	68 (38.2)	
Day 3 FSH (IU/ml)	6.8 (4.9-9.8)	8.8 (7.6-11.4)	6.8 (5.7-8.2)	0.007 [†]
				P1: 1.0
				P2: 0.005
				P3: 0.070
AMH level (ng/ml)	3.5 (2.8-6.3)	2.2 (1.3-3.7)	3.2 (1.8-5.0)	0.056
Sperm concentration ($\times 10^6$ /ml)	49.0 (35.5-77.0)	37.0 (26.5-60.2)	53.0 (32.0-80.7)	0.347
Progressive motility (%)	44.0 (27.5-59.5)	32.5 (23.2-36.7)	39.0 (29.0-54.0)	0.135
TPMS ($\times 10^6$)	54.0 (30.4-102.0)	25.0 (10.4-61.7)	48.5 (23.1-95.0)	0.135

*Data are presented as median (25th-75th percentile), [†]P1 rFSH versus HP-FSH group; P2 HP-hMG versus HP-FSH group; P3 rFSH versus HP-hMG group. [‡]IUI: Intrauterine insemination, FSH: Follicle stimulating hormone, AMH: Anti-Mullerian hormone, TPMS: Total progressive motile sperm count, BMI: Body mass index, HP-hMG: Highly purified human menopausal gonadotropin, HP-FSH: Highly purified FSH

Table 3: Controlled ovarian stimulation outcomes

Characteristics*	rFSH group (n=36)	HP-hMG group (n=23)	HP-FSH group (n=178)	P
Duration of stimulation (days)	9.0 (8.0-11.7)	10.0 (7.0-12.0)	10.0 (8.0-12.0)	0.085
Total gonadotropin dose (IU)	450.0 (375.0-600.0)	450.0 (300.0-600.0)	450.0 (300.0-675.0)	0.674
Endometrial thickness on the day of hCG (mm)	9.0 (8.4-10.2)	9.0 (7.5-10.8)	9.4 (7.8-11.0)	0.633
Follicles ≥ 15 mm on the day of hCG, n (%)				
1	19 (52.8)	17 (73.9)	90 (50.6)	0.112
2	17 (47.2)	6 (26.1)	88 (49.4)	
Biochemical pregnancy rate (%)	19.4	21.7	11.2	0.201
Clinical pregnancy rate (%)	16.7	13.0	9.6	0.435
Live birth rate (%)	16.7	13.0	8.4	0.290
Twin pregnancy, n (%)	0	0	2 (10)	
Miscarriage rate, n (%)	1 (14)	2 (40)	5 (25)	0.597
OHSS rate, n (%)	0	0	0	NS

*Data are presented as median (25th-75th percentile) and n (%). [†]hCG: Human chorionic gonadotropin, OHSS: Ovarian hyperstimulation syndrome, NS: Not statistically significant, rFSH: Recombinant FSH, HP-hMG: Highly purified human menopausal gonadotropin, HP-FSH: Highly purified FSH

HP-hMG group and 25% in HP-FSH group. There was no statistically significant difference amongst groups regarding miscarriage rates ($P = 0.597$). There were two twin gestations in the study population, and both were in the HP-FSH group. One of the twin gestations ended in miscarriage and the other ended with the birth of two healthy babies.

DISCUSSION

IUI is a widely used first-line treatment protocol for infertile couples. It is simple and minimally invasive but has low success rates. Factors affecting IUI success have been studied extensively. Female age, BMI, smoking status, infertility aetiology, and duration, number of previous trials, semen characteristics were all found to affect IUI outcome.^[4,5,20,23] Most of these factors cannot be modified or are patient-dependent. The type of gonadotropin used for COS would be a modifiable factor to improve IUI success if proven to be effective. Our results have shown that ovarian stimulation with rFSH, HP-FSH, and HP-hMG yielded comparable COS characteristics, including similar duration of stimulation, total gonadotropin dose, and endometrial thickness. Furthermore, there was no significant difference between different gonadotropin protocols regarding clinical pregnancy rates (CPR) and LBRs.

IUI is a simple and low-cost treatment option, with low pregnancy rates. Several studies reported CPR per IUI cycle ranging from 8% to 22%.^[4] Indeed, we found a CPR of 11% and an LBR of 10% in 237 IUI cycles in the present study. When cycles were grouped according to the gonadotropin type; LBR was 17% for cycles with rFSH, 8% for cycles with HP-FSH, and 13% for cycles with HP-hMG, with no statistically significant difference between them. In line with our results, most studies also found similar pregnancy rates between different gonadotropins used for COS + IUI cycles.^[14,15,18,20] Therefore, our findings further support the idea that COS protocols with different gonadotropins yield similar reproductive outcomes in IUI cycles.

On the other hand, several studies showed a significantly higher pregnancy rate in COS + IUI cycles with certain gonadotropin types.^[19,21] Demiroglu *et al.* compared rFSH, HMG and hpFSH use in COS + IUI cycles for UEI and found a significantly higher CPR in the rFSH group.^[19] In this study, the number of dominant follicles was significantly higher in the rFSH group. The higher CPR observed in the rFSH group might be attributed to a higher number of preovulatory follicles as previous studies showed that multi follicular growth is associated with an increase in pregnancy rates in IUI cycles.^[24] Indeed, rFSH is more effective in providing a

high ovarian response and a higher number of oocytes were obtained in ART cycles with rFSH use.^[25] Multi follicular development might lead to a higher pregnancy in IUI cycles with rFSH use. However, where the maximum number of preovulatory follicles is limited to 1 or 2 follicles as in the present study, our findings suggest that rFSH does not achieve better pregnancy rates.

Regarding the potency of different gonadotropins, several studies have shown greater potency of rFSH.^[17,19] In a study by Matorras *et al.* comparing rFSH and HP-FSH, there was no difference in terms of stimulation time, insemination day as in our study. However, the number of FSH ampoules consumed per cycle was significantly lower and the estradiol/FSH ampoule ratio was significantly higher in the rFSH group.^[17] The authors suggested that rFSH has a higher potency than HP-FSH. Regarding the potency, we found a similar duration of stimulation, total dose of gonadotropin used, and number of follicles above 15 mm diameter suggesting similar COS characteristics of three gonadotropin types. In line with our findings, Sagnella *et al.* compared COS + IUI cycles with rFSH or HP-hMG and found no statistically significant difference between the groups in terms of clinical pregnancy rates, mean gonadotropin dose, and stimulation length.^[18] Importantly, this research found significantly increased ovarian hyperstimulation syndrome (OHSS) risk in patients who underwent COS with rFSH. Moro *et al.* also found HP-hMG safer than rFSH regarding OHSS risk with comparable pregnancy rates.^[15] In the present study, no cases of OHSS occurred. A possible explanation for this finding was strictly obeying the IUI cancellation policy and withholding hCG in any cycle where more than two follicles develop. However, during the study period, there were cancelled cycles with hyper-response where OHSS risk was high. Unfortunately, the cancelled cycles were not recorded in hospital records. Therefore, this zero OHSS finding in our study does not reflect the actual OHSS risk. Regrettably, we could not make the actual OHSS risk comparison amongst different gonadotropin types due to the absence of records.

In most studies, there was a predilection toward rFSH use for COS.^[14,20,21] In contrast, HP-FSH was the main gonadotropin used in our study, it was used in 75% of the cycles. The reason for this preference in our cycles was the lower cost of HP-FSH. A statistical model developed by Gerli *et al.* has shown that HP-FSH use is more cost-effective than rFSH in COS + IUI cycles.^[26] Furthermore, the same authors conducted an RCT comparing rFSH and HP-FSH use in COS + IUI cycles and found comparable delivery rates with a

lower cost per cycle in favour of HP-FSH.^[27] Because COS + IUI cycles using rFSH, HP-FSH or HP-hMG has similar pregnancy rates, other factors such as cost-effectivity or OHSS risk should be considered while choosing the gonadotropin type for COS + IUI.

The strength of our study is that it will be one of the few studies in the literature comparing the three main gonadotropins used in IUI + COS cycles within the same study. The main limitations of our study were its retrospective nature, small sample size and lack of power analysis. Another limitation was the absence of data regarding cancelled cycles. More prospective studies and large meta-analyses are needed on the subject.

CONCLUSIONS

There was no significant difference in CPR and LBR amongst cycles with different gonadotropins suggesting all three gonadotropin types (rFSH, HP-FSH, HP-hMG) are similarly effective in COS + IUI cycles. Other factors rather than pregnancy rates should be taken into account while choosing the gonadotropin type for COS + IUI.

Authors' contributions

OSYC was responsible for the design of the work, analysed and interpreted the patient data and made critical revision of the manuscript. MD reviewed the literature and was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

Reporting guidelines

The manuscript adheres to the STROBE reporting guidelines.

Data availability statement

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

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Conflicts of interest

There are no conflicts of interest.

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