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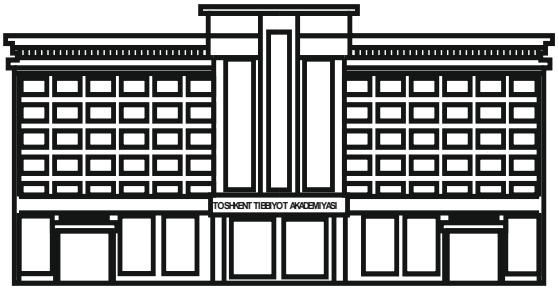

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Тошкент

COMPARATIVE ANALYSIS OF RFSH AND HMG FOR CONTROLLED OVARIAN STIMULATION IN IVF: A RETROSPECTIVE COHORT STUDY

Atakhadjaeva F.A., Dilrabo T. Kayumova, Muhayyo M. Maqsudova, Ranokhon M. Nabieva

Objective: *This retrospective cohort study aims to compare the efficacy and outcomes of controlled ovarian stimulation (COS) in women undergoing in vitro fertilization (IVF) with recombinant follicle-stimulating hormone (rFSH) and purified menopausal gonadotropin (hMG).* ***Methods:*** *A total of 151 infertile women from 'Siz ona bo'lasiz' IVF clinic were included in the study. The primary endpoints were the quantity of mature oocytes retrieved, and secondary endpoints included the duration and dosage of gonadotropin administration. Patients were assigned to three groups: Group A (rFSH), Group B (hMG), and Group C (combination of rFSH and hMG). Stimulation protocols and outcomes were analyzed using statistical methods.* ***Results:*** *The study showed no significant differences in stimulation duration between Groups A and B. However, the combination group (Group C) exhibited a slightly higher duration. In the rFSH group, a notable increase in the number of mature oocytes was observed compared to the hMG group, both at the initial and overall doses. The combination group demonstrated a significant increase in mature oocytes compared to Groups A and B, but with a longer stimulation duration and higher total dosage.* ***Conclusion:*** *The study suggests a negligible difference in the effectiveness of rFSH and hMG for controlled ovarian stimulation in IVF. However, rFSH may have an advantage in terms of efficacy, especially concerning dosage. The combination of rFSH and hMG showed increased oocyte yield but with extended stimulation duration and higher total dosage. Individualized treatment considerations are crucial, and further research is needed to validate these findings.*

Keywords: *IVF, controlled ovarian stimulation, recombinant FSH, human menopausal gonadotropin, infertility, gonadotropin dosage, mature oocytes.*

Assisted reproductive technology (ART) treatments have evolved with the goal of achieving optimal outcomes, emphasizing the need for individualized approaches based on patient characteristics [1–4]. In the context of in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) procedures, the selection of exogenous gonadotropins for controlled ovarian stimulation (COS) becomes a critical determinant. It is paramount to not only consider the general advantages of gonadotropins, such as efficacy, but also to address individual risk factors, encompassing safety concerns, economic efficiency, and overall patient feasibility.

Gonadotropins, pivotal in inducing ovulation, play a central role in the intricate endocrine system governing growth, sexual development, and reproductive function. The primary exogenous gonadotropins employed in IVF/ICSI—follicle-stimulating hormone (FSH), luteinizing hormone (LH), and human chorionic gonadotropin (hCG)—are now available in both urinary and recombinant forms, with the exception of LH [5].

This study delves into the efficacy of recombinant alpha follicle-stimulating hormone (rFSH) when used in conjunction with menopausal gonadotropin (hMG). Human Menopausal Gonadotrophins (hMG), FSH, and LH, derived from human urine collected from postmenopausal women since 1953, can be administered intra-muscularly (IM) or subcutaneously (SC). Postmenopausal urine reflects the hypergonadotropic state of menopause, containing elevated levels of FSH and LH, along with a mixture of these gonadotropins and other protein substances, including small amounts of human chorionic gonadotropin (hCG) [6].

In contrast, rFSH, utilized in infertility management for the past decade, represents a virtually pure compound with excellent batch-to-batch consistency and the ability for large-scale production. The production process involves transfection of cultivated mammalian cells, clonal selection, cell banking, and rigorous large-scale production processes [7]. Uzbekistan has widely adopted and utilized recombinant alpha FSH in infertility treatment.

A persisting debate surrounds the choice between human menopausal gonadotropin and rFSH. A Cochrane meta-analysis, involving 3197 women, reported significantly fewer live births after rFSH compared to hMG for ovarian stimulation (OS), although no significant difference in ovarian hyperstimulation syndrome (OHSS) rates was observed [8].

Subsequent randomized controlled trials (RCTs) have yielded diverse results, with one RCT suggesting that highly purified hMG is at least as effective as rFSH in GnRH antagonist cycles regarding cumulative live birth rate [9]. Another recent RCT found no significant differences in live birth rates between hMG and rFSH for OS [10].

Given the profound impact of oocyte quantity on cumulative live birth rates and IVF success across all female age groups, especially in poor responders (according to POSEIDON criteria), the selection of a superior gonadotropin for optimal follicular response remains a critical consideration [5, 11].

The primary objective of this study is to meticulously assess the methodologies and efficacy associated with administering rFSH and hMG in Controlled Ovarian Stimulation Procedures, contributing valuable insights to the ongoing discourse on gonadotropin selection in ART.

Material and methods

Study design. At the in vitro fertilization (IVF) clinic known as 'Siz ona bo'lasiz,' a single-centre, retrospective cohort study was conducted, involving 151 infertile women. Primary endpoints encompassed the yield of mature oocytes, while secondary endpoints involved the duration and dosage of gonadotropin administration. The outcomes were computed utilizing the online platform https://www.medcalc.org, relying on the student's t-criterion, P-value, RR, OR, and a 95% Confidence Interval.

Patients

The inclusion criteria were defined as follows: participants were required to be within the age range of 18 to 39 years, exhibit regular ovulatory menstrual cycles lasting 24 to 38 days, and present infertility attributed to factors such as tubal issues, male factors, endocrine abnormalities, mild endometriosis, or unexplained causes. Additionally, participants were expected to have early follicular phase serum FSH levels within normal ranges, possess both ovaries, have undergone no more than three previous assisted conception cycles, refrain from assisted conception treatment for at least one complete menstrual cycle, maintain a normal uterine cavity, and provide a signed, written consent form.

The exclusion criteria encompassed the following: the presence of clinically relevant systemic diseases, a history of pregnancy within the preceding three months, a body mass index exceeding 30, a previous occurrence of severe ovarian hyperstimulation syndrome, prior failures in in vitro fertilization (IVF) attributable to fertilization issues or inadequate response to gonadotrophin therapy, abnormal bleeding from the reproductive tract, previous history of chemotherapy or radiotherapy, hypersensitivity to any of the products included in the study.

Patients were randomly assigned to one of the following three groups through an open method:

Group A: 150 IU/day or 225 IU/day or 300 IU/day of HP-hMG

Group B: 150 IU/day or 225 IU/day or 300 IU/day of rFSH

Group C: Combination of HP-hMG and rFSH.

Stimulation protocols

Group A: Start stimulation (day 2 of cycle ± 1 day) with 150 IU/day or 225 IU/day or 300 IU/day of HP-hMG administered subcutaneously (sc.) till administration of trigger. The dose remained fixed to the end of the stimulation. The monitoring of daily follicular growth was conducted through the aid of transvaginal ultrasonography. The administration of progesterone commenced upon the majority of developing follicles reaching a size greater than or equal to 16-18 mm and continued until the day of oocyte retrieval. Final oocyte maturation is triggered at sizes of several of the leading follicles between 16-22 mm. GnRH agonists or hCG are utilized as triggers (Figure 1).

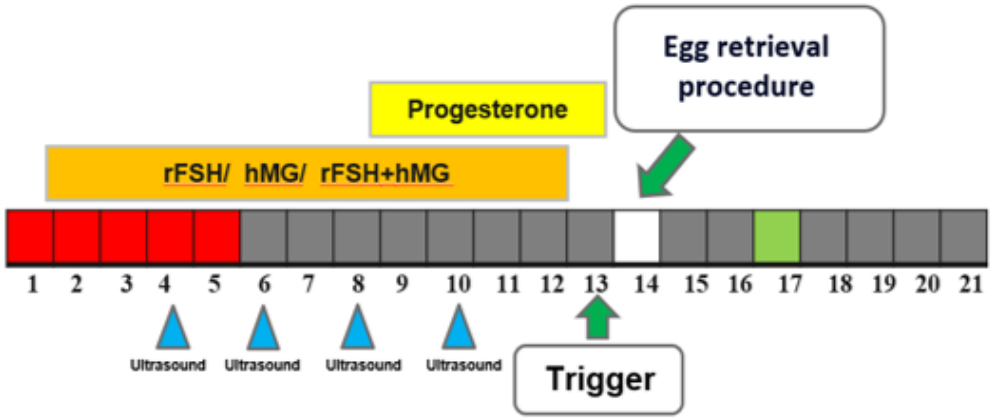

Figure 1. The progestin protocol scheme employed in the study

Group B: Start stimulation (day 2 of cycle ± 1 day) with 150 IU/day or 225 IU/day or 300 IU/day of rFSH administered subcutaneously (sc.) till administration of trigger. The dose remained fixed to the end of the stimulation. The monitoring of daily follicular growth was conducted through the aid of transvaginal ultrasonography. The administration of progesterone commenced upon the majority of developing follicles reaching a size greater than or equal to 16-18 mm and continued until the day of oocyte retrieval. Final oocyte maturation is triggered at sizes of several of the leading follicles between 16-22 mm. GnRH agonists or hCG are utilized as triggers.

Group C: Start stimulation (day 2 of cycle ± 1 day) with any combination of HP-hMG and rFSH administered subcutaneously (sc.) till administration of trigger. The gonadotropin dosage is variable. The monitoring of daily follicular growth was conducted through the aid of transvaginal ultrasonography. The administration of progesterone commenced upon the majority of developing follicles reaching a size greater than or equal to 16-18 mm and continued until the day of oocyte retrieval. Final oocyte maturation is triggered at sizes of several of the leading follicles between 16-22 mm. GnRH agonists or hCG are utilized as triggers.

Results

A total of 151 female participants underwent ovarian stimulation for the research. Out of these, in open method, 101 were assigned to Group A (rFSH), 26 to Group B (hMG), and 23 patients to Group C (rFSH+hMG). Figure 2 depicts the profile of the enrolled women in the study.

When examining the clinical characteristics of the recruited women for the study, no significant inter-group differences were observed in terms of age. However, the duration of infertility was found to be higher in the group of women receiving menopausal gonadotropin compared to the rFSH group. In our combination group, the duration of infertility was notably lower compared to both groups in an intriguing manner. No significant differences were identified in the type of infertility during the analysis of infertility characteristics (Table 1).

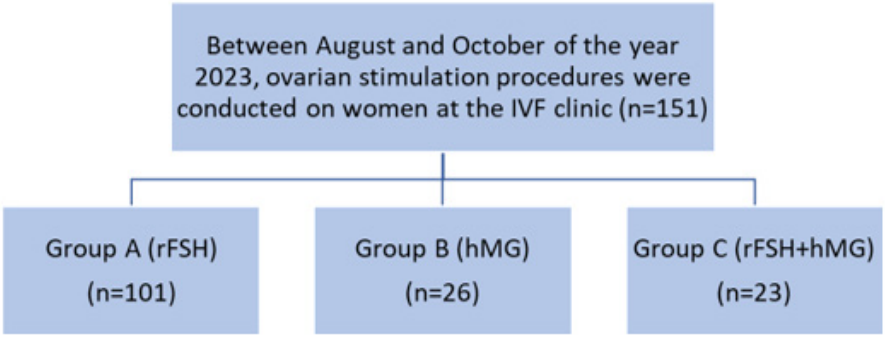

Figure 2. Flowchart of the study comparing rFSH and hMG

Table 1.

Clinical characteristics of the recruited women for the study

	Group A (rFSH) n=101	Group B (hMG) n=26	Group C (rFSH+hMG) n=23	P1*	P2**
Age (years), M±m	31,6±0,6	32,6±1,1	31,1±1,2	<0.0001	=0.0044
Duration of infertility (years), M±m	6,3±0,4	7,8±1,0	4,8±0,5	<0.0001	<0.0001
Type of infertility:					
Primary	56 (55,9%)	12 (42,6%)	12 (52,2%)	=0.2273	=0.7484
Secondary	55 (44,1%)	14 (53,8%)	11 (47,8%)	=0.3781	=0.7484

**** P-value was calculated for A and B groups; ** P-value was calculated for A and C groups***

When investigating the causes leading to infertility, tubal-peritoneal factor predominated in all groups. Subsequently, male factor infertility was nearly equally distributed among all groups, while the reduced ovarian reserve was identified to be relatively lower in Group B compared to Groups A and C (Table 2).

Table 2.

Causes of infertility

	Group A (rFSH) n=101	*Group B (hMG) n=26*	*Group C (rFSH+hMG) n=23*	*P1**	*P2***
Tubal-peritoneal factor	***42 (41,2%)***	***9 (34,6%)***	***9 (39,2%)***	***=0.5415***	***= 0.8608***
Male factor	***21 (20,6%)***	***5 (19,2%)***	***5 (21,8%)***	***= 0.8748***	***= 0.8986***
Reduced ovarian reserve	***37 (36,8%)***	***5 (19,2%)***	***7 (30,5)***	***= 0.0905***	***= 0.5707***
Endocrine factors	***7 (7,4%)***	***9 (34,6%)***	***4 (17,4%)***	***= 0.0002***	***= 0.1369***
Associated with endometriosis	***19 (19,1%)***	***7 (26,9%)***	***4 (17,4%)***	***= 0.3832***	***= 0.8512***
Ideopatic	***13 (13,2%)***	***2 (7,7%)***	***3 (13%)***	***=0.4445***	***= 0.9797***

**** P-value was calculated for A and B groups; ** P-value was calculated for A and C groups***

The duration of stimulation did not exhibit significant differences between Groups A and B, whereas in our combination group, a slightly higher duration of 11.6±0.9 days was recorded. In the rFSH group, the incidence of achieving a higher number of mature oocytes was observed to be 10.67% at the initial dose and 15.3% at the overall dose compared to the hMG group. Notably, a 14.3% increase in the attainment of numerous mature oocytes was observed. In our combination Group C, however, there was a substantial increase of 40.9% and 61% compared to Groups A and B, respectively, in the number of mature oocytes obtained. Nonetheless, the stimulation duration, as well as the initial and overall doses of the administered preparations, were significantly higher (Table 3).

The combination of rFSH and hMG was primarily utilized in women with a documented gynecological history, who had undergone surgeries related to ovaries and fallopian tubes. Among the 23 women in the group subjected to ovarian stimulation, favorable outcomes were achieved even in the presence of expected gynecological history, with an average of 12.4±2.4 mature oocytes obtained. When compared to Groups A and B, our women demonstrated significantly higher results (41% and 61%, respectively) despite the absence of significant gynecological history. However, the stimulation duration was prolonged (11.6±0.9 days), and the total dosage of administered medications (2364.1±123.8) was elevated. This constitutes the negative aspect of the process.

Table 3.

The Characteristics of the Controlled Ovarian Stimulation Process

	Group A (rFSH) n=101	Group B (hMG) n=26	Group C (rFSH+hMG) n=23	P1*	P2**
Stimulation duration, day, M±m	9,0±0,3	9,2±0,7	11,6±0,9	=0.0292	<0.0001
Initial dose, IU, M±m	190,3±5,1	210,6±8,3	231,5±12,4	<0.0001	<0.0001
Overall dose, IU, M±m	1696,3±67	1955,8±156,6	2364,1±123,8	<0.0001	<0.0001
Retrieved mature oocytes, M±m	8,8±1,1	7,7±1,3	12,4±2,4	<0.0001	<0.0001

** P-value was calculated for A and B groups; ** P-value was calculated for A and C groups*

Discussion

The primary aim of this research is to evaluate the procedural methods and effectiveness associated with the administration of Recombinant Follicle-Stimulating Hormone (rFSH) and Purified Menopausal Gonadotropin (hMG) in the context of Controlled Ovarian Stimulation procedures.

According to our findings, there is nearly no significant difference in the efficacy when using two different types of gonadotropins for controlled ovarian stimulation in the practice of IVF. However, it is noteworthy that rFSH may exhibit a noticeable efficacy advantage compared to hMG, particularly concerning both the initial and overall dosage. Furthermore, when considering the utilization of a combination of rFSH and hMG, a higher duration of stimulation and an elevated total administered dosage correlated with a notably increased number of obtained mature oocytes.

According to the results of a similarly conducted study, out of the 30,630 IVF cycles analyzed in this review, 74% utilized rFSH, while 26% opted for hMG-HP. A statistically significant discrepancy in drug utilization per cycle was observed, with rFSH demonstrating a substantially lower usage compared to hMG-HP (2072.53 +/- 76.73 IU vs. 2540.14 +/- 883.08 IU, indicating a 22.6% higher consumption for hMG-HP; $p < 0.01$). Furthermore, the median starting dose exhibited a significant reduction for rFSH in comparison to hMG-HP (150 IU vs. 225 IU, representing a 50% higher starting dose for hMG-HP; $p < 0.01$). The mean oocyte yield per IVF cycle among patients treated with rFSH was significantly higher than those treated with hMG-HP (10.80 +/- 6.02 vs. 9.77 +/- 5.53; $p < 0.01$). Similarly, the average mature oocyte yield was also notably greater in the rFSH group compared to the hMG-HP group (8.58 +/- 5.27 vs. 7.72 +/- 4.59; $p < 0.01$) (Geoffrey H Trew at al., 2010).

Similar opinions have been provided in subsequent evaluations that align with our findings. In patients aged less than 35 years, the FSH alone group exhibited a significantly higher number of retrieved oocytes compared to the FSH-hMG group (13.7 vs. 9.2, $P = 0.04$), with no observed differences in other age groups. Additionally, the FSH-hMG group necessitated a significantly higher dosage of gonadotropins across all age categories (all ages, $P < 0.001$; <35 years, $P = 0.013$; ≥35 years, $P < 0.001$) (Chisa Tabata at al., 2015).

In summary, when considering the conclusions, our presented results are in line with subsequent investigations, yielding consistent outcomes. In the context of IVF procedures involving ovarian stimulation, the selection of gonadotropins must take into account the individual characteristics of each patient, emphasizing their importance. In our center, randomized trials are being planned under the conditions of Uzbekistan. However, larger-scale studies are required to validate such findings.

Acknowledgments:

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Conflict of Interest:

The authors declare no conflicts of interest related to this study.

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