ARAŞTIRMA MAKALESİ / RESEARCH ARTICLE

Kocaeli Med J 2023;12(3):363-369, doi: 10.5505/ktd.2023.40221

Polikistik Over Sendromu Olmayan Fazla Kilolu veya Obez Kadınlarda rFSH, rFSH+rLH ve HP-HMG Preparatlarının Yardımcı Üreme Teknolojisi Sonuçları Üzerindeki Etkilerinin Karşılaştırılması

Comparison of The Effects of rFSH, rFSH+rLH and HP-HMG Preparations on Assisted Reproductive Technology Outcomes in Overweight or Obese Women without Polycystic Ovary Syndrome

Merve Demir[1], Özge Senem Yücel Çiçek[1], Emre Sertel[1], Leylim Yalçınkaya[1], Sare Doğan[1], Osman Onur Daloğlu[2], Emek Doğer[1], Birol Vural[1]

[1]Kocaeli Üniversitesi Tıp Fakültesi, Kadın Hastalıkları ve Doğum Ana Bilim Dalı, İstanbul, Türkiye.

[2]Sağlık Bilimleri Üniversitesi Bursa Yüksek İhtisas Eğitim ve Araştırma Hastanesi, İç Hastalıkları Ana bilim Dalı, Endokrinoloji ve Metabolizma Hastalıkları, Bursa, Türkiye.

ÖZ

Giriş: Bu çalışmanın amacı polikistik over sendromu (PKOS) olmayan obez veya fazla kilolu hastalarda yardımcı üreme teknolojisi (YÜT) uygulamalarında rFSH, rFSH+rLH ve HP-HMG kullanımının sonuçlarını karşılaştırmaktır.

Yöntem: Bu retrospektif kohort çalışması, YÜT sırasında GnRH antagonist protokolü ile over stimülasyonu uygulanan PKOS'suz ancak vücut kitle indeksi 25'in üzerinde olan kadınlarla yürütüldü. Bu hastaların uygun siklusları kullanılan gonadotropin tipine göre rFSH, rFSH+rLH ve HP-HMG olmak üzere üç gruba ayrıldı. YÜT sonuçları bu üç grup arasında karşılaştırıldı.

Bulgular: Devam eden gebelik oranı ve 1. derece embriyo oranı rFSH+rLH grubunda (sırasıyla %41.2 ve %71.7) rFSH grubuna göre (sırasıyla %14.3 ve %47.2) istatistiksel olarak daha yüksekti. rFSH alan grup ile HP-HMG alan grup arasında ve rFSH+rLH alan grup ile HP-HMG alan grup arasında devam eden gebelik oranı ve grade 1 embriyo oranı açısından istatistiksel fark yoktu. Ayrıca HCG günü endometrial kalınlık rFSH+rLH grubunda HP-HMG grubuna göre istatistiksel olarak anlamlı derecede yüksekti.

Sonuç: PKOS'suz obez veya fazla kilolu hastalarda rFSH+rLH kombinasyonunun embriyo kalitesi ve devam eden gebelik üzerinde tek başına rFSH'ye göre üstün etkisi vardır. Ayrıca hCG gününde bu hastaların endometriyumunun rFSH+rLH kullanıldığında HP-HMG kullanıldığı duruma göre daha kalın olduğu görülmektedir.

Anahtar Kelimeler: obezite, insan menopozal gonadotropin, rekombinant LH, yardımcı üreme teknolojisi

ABSTRACT

Objective: The aim of this study is to compare the results of using rFSH, rFSH+rLH and HP-HMG in assisted reproductive technology (ART) applications in obese or overweight patients without polycystic ovary syndrome (PCOS).

Method: This retrospective cohort study was conducted with women without PCOS but with a body mass index greater than 25 who underwent ovarian stimulation with the GnRH antagonist protocol during ART. Appropriate cycles of these patients were divided into three groups as rFSH, rFSH+rLH and HP-HMG according to the type of gonadotropin used. ART outcomes were compared between these three groups.

Results: Ongoing pregnancy rate and grade 1 embryo rate were statistically higher in the rFSH+rLH group (41.2% and 71.7%, respectively) than in the rFSH group (14.3% and 47.2%, respectively). There was no statistical difference between the group that received rFSH and the group that received HP-HMG, and between the group that received rFSH+rLH and the group that received HP-HMG in terms of ongoing pregnancy rate and grade 1 embryo ratio. In addition, the endometrial thickness on the day of HCG was statistically significantly higher in the rFSH+rLH group compared to the HP-HMG group.

Conclusion: The rFSH+rLH combination has a superior effect over rFSH alone on embryo quality and ongoing pregnancy in obese or overweight patients without PCOS. In addition, it is seen that the endometrium of these patients on the hCG day is thicker when rFSH+rLH is used than when HP-HMG is used.

Keywords: obesity, human menopausal gonadotropin, recombinant LH, assisted reproductive technology

Gönderim Tarihi: 22.08.2023 **Kabul Tarihi:** 28.12.2023

Correspondence: Uzm. Dr. Merve Demir, Kocaeli Üniversitesi Tıp Fakültesi, Kadın Hastalıkları ve Doğum Ana Bilim Dalı, İstanbul, Türkiye.
E-mail: mervedemir_yeditepe@hotmail.com

Atıf/ Cite as: Demir M., Yücel Cicek OS., Sertel E., Yalçinkaya L., Dogan S., Daloglu OO., Doger E., Vural B. Comparison of The Effects of rFSH, rFSH+rLH and HP-HMG Preparations on Assisted Reproductive Technology Outcomes in Overweight or Obese Women without Polycystic Ovary Syndrome . Kocaeli Med J 2023;12(3):363-369 doi: 10.5505/ktd.2023.40221

INTRODUCTION

Obesity causes many chronic diseases. In addition, it negatively affects fertility and the results of assisted reproductive technology (ART) treatments. (ART) (1-3). It was determined that overweight and obese women (Body Mass Index ≥ 25 kg/m2) had a lower chance of live birth after ART treatment compared to normal weight women (4). Therefore, there is a need for protocols that will increase the chance of success in ART applications in obese and overweight patients.

Polycystic ovary syndrome (PCOS) is characterized by high luteinizing hormone (LH) levels. The reason for this may be the persistently rapid gonadotropin-releasing hormone (GnRH) pulse frequency due to progesterone deficiency that develops in parallel with chronic anovulation. In these patients, an increase in follicle stimulating hormone (FSH) levels is not observed as in LH (5). In overweight and obese individuals, a serious leptin resistance and impairment in leptin activity may occur, resulting in irregularity and decrease in GnRH secretion and a decrease in LH pulse amplitude. Central leptin resistance may be a potential mechanism for decreased LH levels and hypogonadotropic state in obese and overweight individuals (6,7). Reducing the frequency of GnRH secretion, which may develop due to leptin resistance in overweight individuals without polycystic ovary syndrome, may reduce LH secretion. Subclinical endogenous LH deficiency has been shown in some studies in obese and overweight patients without PCOS (8-11). Therefore, adding LH-containing preparations to ovarian stimulation protocols during ART to be applied in these patients may positively affect the success of the treatment.

For the purpose of LH supplementation during ART, recombinant LH (rLH, lutropin alfa) can be added to recombinant FSH (rFSH) or a urine extract human menopausal gonadotropin (HMG, menotropin) preparation containing both FSH and LH can be used. rLH is structurally and functionally similar to endogenous human LH. Different HMG preparations may differ in LH bioactivity due to increased purification and greater LH loss (12). The ratio of recombinant FSH and recombinant LH in combination is usually 2:1. Recently, recombinant FSH and recombinant LH have been combined in a single product (Pergoveris; follitropin alfa/lutropin alfa 150 IU/75 IU), thus allowing administration of both gonadotropins in a single injection (13).

The aim of this study was to compare the results of using rFSH, rFSH+rLH, and HP-HMG for ART in patients with a body mass index (BMI) over 25 and without PCOS. We aimed to investigate whether exogenous LH supplementation is beneficial in these patients and if so, which gonadotropin preparation should be used.

MATERIALS AND METHODS

Study design and participants

This retrospective cohort study was conducted in Kocaeli University Medical Faculty Assisted Reproductive Techniques Clinic with obese and overweight non-PCOS patients who underwent intracytoplasmic sperm injection (ICSI) with controlled ovarian stimulation (COS) between 2016-2021. The study was approved by Kocaeli University Ethics Committee (Project number: 2021/295). Informed consent was obtained from the patients for the use of data, and the study was conducted in accordance with the Declaration of Helsinki.

Patients who did not become pregnant despite having at least one year of unprotected sexual intercourse, had a body mass index above 25 and a baseline FSH level of less than 20 were included in the study. In addition, patients who underwent COS with rFSH or rFSH+rLH or highly purified human menotropin (HP-HMG) and underwent fresh embryo transfer were included in the study. The Rotterdam criteria (2003 revision) were used for the diagnosis of PCOS (14).

Patients who did not undergo embryo transfer for any reason, were diagnosed with PCOS, and had endometrioma in ultrasonography (USG) were excluded from the study.

Outcome measures

The primary outcomes of the study were the ongoing pregnancy rate (OPR), clinical pregnancy rate (CPR) and chemical pregnancy rate.

Secondary outcomes were the number of good quality embryos, total gonadotropin dose, some biochemical and ultrasonographic values on the day of HCG, metaphase II (MII) oocyte percentage, and fertilization rate.

Protocol

A total of 99 patients who underwent COS with the GnRH antagonist protocol during ART between January 2016 and April 2021 were included in the study. Appropriate cycles of these patients were divided into three groups as rFSH (n=35), rFSH+rLH (n=34) and HP-HMG (n=30) according to the type of gonadotropin used.

Demographic information included age, body mass index (BMI) and cause of infertility were collected from hospital records and compared between groups. Baseline assessments of patients at the beginning of the menstrual cycle (evoked or spontaneous) such as serum FSH, LH, estradiol, Anti-Müllerian hormone (AMH), and antral follicle count (AFC) were also obtained from the records and compared between groups.

All patients underwent COS with GnRH antagonist protocol. Daily gonadotropin injections were started in patients with endometrial thickness <5 mm and follicle >10 mm according to transvaginal USG performed on the 3rd day of the menstrual cycle. rFSH (Gonal-F®, Merck Serono, Aubonne, Switzerland and Puregon®, Organon, The Netherlands), rLH (Luveris, Serono, Switzerland) added to rFSH or HP-HMG (Menopur®; Ferring, Saint-Prex, Switzerland) were used as gonadotropins. Initial and subsequent gonadotropin doses were determined according to age, BMI, AMH level, current follicle development, and previous stimulus response. Follicular development was followed with the transvaginal USG. When the leading follicle diameter reached 12 mm, 250 µg cetrorelix acetate (Cetrotide vial 0.25 mg, Baxter Oncology GmbH, Frankfurt, Germany) was started to be administered daily. When the diameter of at least three follicles reached 17 mm, 250 µg recombinant hCG (Ovitrelle, Merck-Serono, Modugno, Italy) was administered and oocyte retrieval was performed 34-36 hours after recombinant hCG application. Oocytes were fertilized by ICSI.

Embryos in our study were evaluated according to the scoring system in the study published by Blank et al. in 2020 (15). These scoring systems by Blank et al. (15) were created according to Alpha and ESHRE scoring criteria (16), Gardner's scoring criteria (17) and local guidelines (18,19) described in previous studies. In this study, embryos were classified as

excellent, good, fair, and poor. Embryos of excellent quality were determined as grade 1, good quality embryos as grade 2, and fair quality embryos as grade 3. Grade 1 (excellent) Day 3 embryo (68 ± 1 hour after fertilization) was considered an embryo with 8 equally sized mononuclear blastomeres with <10% fragmentation. Grade 1 (excellent) quality 5th day embryos were considered as 4/5AA and 4/5AB embryos (The number represents the cell stage, the letters represent the Inner Cell Mass (ICM) and Trophetodermin (TE) score, respectively.).

One or two embryos were transferred on the 3rd or 5th day. For luteal phase support, vaginal tablets containing 200 mg progesterone three times a day (Progestan, Koçak Farma, Tekirdag, Turkey) or vaginal gels containing 90 mg progesterone two times a day (Crinone, Fleet Laboratories Limited, Hertfordshire, England) were started.

Total gonadotropin dose, biochemical and ultrasonographic measurements taken on the day of HCG of all patients were compared between groups. The data obtained by examining the embryology records of the patients were compared between the groups.

Pregnancy results of the patients were obtained from the records and compared between the groups. A serum beta hCG level above 20 mIU/mL was considered as a chemical pregnancy. The presence of intrauterine gestational sac 6 weeks after embryo transfer in transvaginal USG was evaluated as clinical pregnancy (CPR). The presence of at least one live fetus at the end of the 12th week following embryo transfer was considered ongoing pregnancy (OPR).

Statistical analysis

IBM SPSS 20.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Whether the variables showed normal distribution was evaluated using the Kolmogorov-Smirnov test or the Shapiro-Wilk test. Numerical variables with normal distribution were shown as mean ± standard deviation, numerical variables with non-normal distribution were shown as median (25th - 75th percentile), and categorical variables were shown as frequency (percentage). Differences between groups were determined by one-way analysis of variance (ANOVA) for normally distributed numerical variables, and the Kruskal-Wallis Test for non-normally distributed numerical variables. Relationships between categorical variables were evaluated by Chi-square analysis and Fisher's exact test. To test two-sided hypotheses, $P < 0.05$ was considered sufficient for statistical significance.

RESULTS

This study was conducted with 99 patients with a body mass index above 25 who underwent ICSI with the antagonist protocol. Of these, rFSH was used as gonadotropin in 35, rFSH+rLH was used as gonadotropin in 34, and HP-HMG was used as gonadotropin in 30 of them. The baseline demographic, clinical and laboratory characteristics of the patients included in this study are shown in Table 1 and these characteristics are compared according to the gonadotropin types used. There was no significant difference between the groups in terms of these characteristics.

The groups formed according to the type of gonadotropin used were compared in Table 2 according to the total gonadotropin dose used, ultrasonographic and laboratory findings on the day of HCG, and embryological results after oocyte retrieval. Endometrial thickness on HCG day was statistically significantly higher in the rFSH+rLH group than in the HP-HMG group.

A total of 149 embryos were transferred to 99 patients, by transferring a single embryo to some of the patients and two embryos to some. In Table 3, the distribution of embryos transferred to the patients was compared between the groups and no significant difference was observed ($p = 0.60$). In addition, the comparison of the groups in terms of embryo quality is shown in Table 4. A statistically significant difference was observed between the groups in terms of embryo quality ($p=0.003$). Statistically significant more grade 1 embryos were obtained in the group using rFSH+rLH compared to the group using only rFSH. There was no significant difference between the groups receiving rFSH and HP-HMG, and the groups receiving rFSH+rLH and HP-HMG in terms of grade 1 embryo ratio. However, without statistical significance, the rate of grade 1 embryos in the group receiving HP-HMG was higher than the rate of grade 1 embryos in the group receiving rFSH.

The comparison of the groups in terms of pregnancy rates is shown in Table 5. Ongoing pregnancy rate was statistically higher in the group receiving rFSH+rLH than in the group receiving only rFSH. There was no significant difference between the groups given rFSH and HP-HMG and the groups given rFSH+rLH and HP-HMG in terms of ongoing pregnancy rate. However, without statistical significance, a higher ongoing pregnancy rate was observed in the group receiving HP-HMG than in the group receiving rFSH. There was no significant difference between the groups in terms of clinical and chemical pregnancy rates.

Table 1. Comparison of Baseline Demographic, Clinical and Laboratory Features of the Patients By Group

PARAMETER	rFSH (n=35)	rFSH+rLH (n=34)	HP-HMG (n=30)	P
Age (years)	33(29-38)	36,5(32-38)	37 (30,5-40,25)	0,234*
BMI (kg/m²)	29,5(27,5-33,69)	29,02(26,35-31,62)	29,9(26,68-34,19)	0,514*
Basal FSH, (IU/L)	7,65(6,65-8,49)	8,16(6,63-9,79)	7,65(5,42-10,16)	0,510*
Basal LH, (mIU/mL)	3,95(2,98-5,4)	4,85 (3,26-6,74)	3,49 (2,4-6,16)	0,102*
Basal TSH (mIU/mL)	1.95 ± 0.95	1.97 ± 0.93	1.84 ± 0.87	0.837**
Antral follicle count (n)	9,00 (6-12)	6,00 (3-10)	7,00 (3-14)	0,103*
AMH (ng/ml)	2,49 (1,19-3,24)	1,38 (0,77-2,70)	1,76 (0,58-3,24)	0,091*
Cause of infertility				
Unexplained	16 (45.7 %)	8 (23.5 %)	11(36.7 %)	
Low ovarian reserve	6 (17.1%)	12 (35.3 %)	10 (33.3 %)	
Tubal factor	3 (8.6 %)	1 (2.9 %)	1 (3.3 %)	**0.368*** **
Male factor	8 (22.9 %)	7 (20.6 %)	5 (16.7 %)	
Female + Male factor	2 (5.7 %)	5 (17.6 %)	3 (10 %)	

Variables are given as median (25 _75 percentile values), mean ±SD and n (%).
* Kruskal-Wallis Test.
** ANOVA test.
*** Fisher's exact test.
Abbreviations: BMI=Body Mass Index, FSH=Follicle Stimulating Hormone, LH=Luteinizing Hormone, TSH=Thyroid Stimulating Hormone, AMH=Anti-Müllerian hormone

Table 2.Comparison of the Groups in Terms of Total Gonadotropin Used, Ultrasonographic and Laboratory Findings on the Day of HCG, Embryological Results After Oocyte Retrieval

PARAMETER	rFSH (n=35)	rFSH+rLH (n=34)	HP-HMG (n=30)	P
Total gonadotropin dose used (IU)	2400 (1950-2775)	2700 (2509,75-3318,75)	3000(2306,25-3606,25)	0.073*
E2 value on HCG day (pg / ml)	1011 (714-1451)	776 (580,75-1263,25)	902 (542,75-1808,75)	0.32*
Progesterone value on HCG day (pg / ml)	0,87 (0,63-1,07)	0,71 (0,45-0,96)	0,69 (0,44-1,08)	0.159*
Endometrial thickness on HCG day (mm)	11,20(±2,18)[ab]	11,77(±2,63)[a]	10,20(±2,30)[b]	***0.033*** **
≥ 12 mm follicle on HCG day (n)	8 (5-9)	6 (4-7)	5 (2,75-9,25)	0.172*
≥ 17 mm follicle on HCG day (n)	2 (2-3)	2,5 (2-3,25)	3,5 (2,75-8)	0.071*
Number of oocytes retrieved (n)	7(5-9)	5,5 (4-7,5)	5,5 (2-10)	0.115*
M2 oocyte count (n)	5 (3-7)	4 (3-7)	4 (2-8)	0.497*
M2 oocyte (%)	78 (58,5-91,5)	81,5(68-100)	85,5(62-100)	0.362*
Embryo transfer day Day 3 Day 5	27 (77.1 %) 8 (6.4 %)	28 (82.4 %) 6 (17.6 %)	26 (86.7 %) 4 (13.3 %)	0.614***
Fertilization rate (%)	75 (52-91,5)	66(55-100)	77,5(50-100)	0.958*

Variables are given as median (25-75 percentile values), mean ±SD or n (%).
* Kruskal-Wallis Test
** ANOVA test.
*** Chi-square test
Bold/italics value signifies statistical significance (p<0.05)
The same superscript letters denote catagories that are not significantly different from each other by the 0.05 level

Table 3.Distribution of the Number of Embryos Transferred to Patients By Groups

	rFSH	rFSH+ rLH	HP-HMG	TOTAL	P
Single embryo transfer	17 (48.6%)	15 (44.1%)	17 (56.7%)	49	0,60*
Double embryo transfer	18 (51.4%)	19 (55.9%)	13 (43.3%)	50	
Total transferred embryo	53	53	43	149	

Variables are given as n (%).
* Chi-square test.

Table 4.Comparison of Groups in Terms of Embryo Quality

	rFSH	rFSH rLH	HP-HMG	TOTAL	P
Grade1	25 (47.2%)[a]	38 (71.7%)[b]	29 (67.4%)[a, b]	92	***0.004****
Grade2	28 (52.8%) [a]	12 (22.6%)[b]	11 (25,6%) [b]	51	
Grade3	0 (0.0%) [a]	3 (5.7%) [a]	3(7%) [a]	6	
Total	53	53	43		

Variables are given as n (%).
* Fisher's exact test.
Bold/italics value signifies statistical significance (p<0.05).
The same superscript letters denote catagories that are not significantly different from each other by the 0.05 level.

Table 5. Comparison of Groups in Terms of Pregnancy Rates Achieved

	rFSH (n=35)	rFSH+rLH (n=34)	HP-HMG (n=30)	P
Chemical pregnancy n(%)	12 (34.3%)	15 (44.1%)	16 (53.3%)	0.302*
Clinical pregnancy n(%)	9 (25.7%)	15 (44.1%)	12 (40%)	0.250*
Ongoing pregnancy n(%)	5 (14.3%)[a]	14 (41.2%)[b]	10 (33.3%)[ab]	***0.042****

Variables are given as n (%).
* Chi-square test
Bold/italics value signifies statistical significance (p<0.05).
The same superscript letters denote catagories that are not significantly different from each other by the 0.05 level.

DISCUSSION

FSH and LH play complementary roles with each other in follicular growth and ovulation events in reproductive medicine (20). Tesarik and Mendoza showed that the inclusion of exogenous LH in ovarian stimulation can lead to increased numbers of mature oocytes and good quality zygotes and embryos compared to stimulation with FSH alone. In addition, they showed that the addition of exogenous LH increased implantation rates in donor groups with pre-stimulation serum LH <1 IU/l (21). In the study of Balash et al., the importance of adding exogenous LH in ovarian stimulation in patients with hypogonadotropic hypogonadism was expressed (22). Today, exogenous LH is given in two forms in the ovarian stimulus. One is recombinant luteinizing hormone (rLH), which is structurally and functionally similar to endogenous human LH, added to rFSH at ovarian stimulus, and the other is human menopausal gonadotropin (HMG, menotropin), a urine extract containing both FSH and LH (12). There have been some studies evaluating the effect of these two preparations on treatment in ART cycles (20,23,24,25,26,27). In these studies, there was no consensus on the superiority of any of the preparations over the other. The effects of two available LH preparations (human menopausal gonadotropin [HMG] and recombinant FSH + recombinant LH) on ovarian stimulation and IVF cycle outcomes were compared in Orvieto's literature review with all relevant articles reporting IVF and intracytoplasmic injection results after ovarian stimulation. There was no statistically significant difference in ovarian stimulation variables and clinical pregnancy and live birth rates between the two groups. In addition, a combined analysis of all available prospective and retrospective studies has not been conclusive in favor of either source of LH bioactivity (13). In addition, in 2 different studies comparing the groups induced by FSH alone, rFSH+rLH, and HMG+rFSH during ART, no significant differences were found in terms of clinical and ongoing pregnancy rates. In other words, induction using different exogenous LH preparations in these studies did not have a significant advantage over each other and induction with FSH alone. Only, it was observed that the total gonadotropin dose used in the study of Tayyar et al. was lower in the rLH+rFSH combination than in the HMG+rFSH combination (12,28). Different HMG preparations are available due to differences in purification (12). We used highly purified menotropin (HP-HMG) in our study.

Although there are various studies in the literature evaluating the superiority of preparations containing exogenous LH over each other or rFSH alone during ovulation induction, there are few studies targeting a specific group that may have endogenous LH deficiency. In our study, we aimed to evaluate the benefit of adding exogenous LH in different preparations during ovulation induction in this patient group, considering that endogenous LH deficiency may develop due to leptin resistance in overweight and obese patients without polycystic ovary syndrome. Although a few recent studies (8,10,11) have shown that endogenous LH deficiency in obese and overweight individuals without PCOS or that ovulation induction with exogenous LH may be beneficial in these individuals, adequate studies have not been conducted on this subject. In addition, it has not been disclosed which pharmacological exogenous LH preparation would be more beneficial to use for ovulation induction in these individuals. In our study, the effects of rFSH, rFSH+rLH and HP-HMG preparations on ART outcomes were compared in obese and overweight

patient groups without polycystic ovary syndrome.

In a study published in 2015 by Vural et al., which excluded patients with polycystic ovary syndrome, it was shown that baseline LH levels were significantly lower in obese patients than in normal-weight patients (8). Similarly, in the medical specialty thesis published in 2019 by the first author of this study, which was performed by excluding individuals with polycystic ovary syndrome (10), and in another article (11) published in 2020 containing the findings of this thesis; LH levels of obese and overweight patients were lower than normal weight patients. In addition, in this studies, it was observed that adding rLH to rFSH during ART in obese and overweight patients had a positive effect on ongoing pregnancy rates and embryo quality. However, the effect of adding rLH was not observed in normal weight patients (10,11). In our current study, the HP-HMG preparation containing FSH and LH together was also evaluated; rFSH, rFSH+rLH combination and HP-HMG preparations were compared with each other during ART in patients without PCOS and with a body mass index above 25. A significant increase was observed in grade 1 embryo quality and ongoing pregnancy rates in induction with rFSH+rLH combination compared to induction with rFSH alone. Although a higher grade 1 embryo quality rate and a higher ongoing pregnancy rate were detected in the group induced with HP-HMG than the group induced with rFSH, this increase was not found to be statistically significant. In addition, in our current study, no significant difference was observed between the groups induced by the combination of HP-HMG and rFSH+rLH in terms of these variables. In other words, the superiority of HP-HMG induction over either rFSH or rFSH+rLH options in ART applications in patients with non-polycystic BMI>25 has not been definitively proven in terms of embryo quality or ongoing pregnancy variables. Therefore, the definitive statistically significant conclusion we have drawn from our study is that rFSH+rLH has a superior effect on embryo quality and ongoing pregnancy in this patient group compared to rFSH alone.

In the study conducted by Revelli et al., published in 2015, including 848 IVF patients, rFSH + rLH (2:1 ratio) and groups receiving HMG were compared. Higher pregnancy rates were found in those who received rFSH+rLH, based on individuals with more than 8 oocytes retrieved (27). Of the 848 patients included in this study, only 3 had anovulation, so the rate of PCOS was quite low. In addition, the mean BMI of the groups included in the study was between 22 and 23 (equivalent to normal weight, close to overweight). Therefore, the sample group of this study is close to the sample group of our study. Although rFSH+rLH was not superior to HMG in our study, it was determined that rFSH+rLH was superior to rFSH in this patient sample in terms of embryo quality and ongoing pregnancy rate, but no superiority of HMG over rFSH in these respects was determined.

In most of the studies in the literature comparing rFSH+rLH and HMG preparations, no significant difference was observed in terms of endometrial thickness. (20,26,27) In our study, endometrial thickness on the day of HCG was statistically significantly higher in the rFSH+rLH group compared to the rHMG group. The difference of our study from other studies is that it was studied with a special group consisting of overweight or obese patients who were not diagnosed with PCOS. The effect of these preparations on endometrial thickness should be evaluated with further studies in this patient group. Because changes in endometrial thickness may affect the success of ART (29).

Our study is one of the few studies in the literature comparing two gonadotropins containing exogenous LH and rFSH containing only FSH in the same study. The strength of our study is that it is one of the first studies in the literature to carry out this study in a specific group thought to have endogenous LH deficiency. The limitations of our study are the retrospective nature of our study, the small sample size, and the lack of data on live births and patients who did not undergo embryo transfer.

In conclusion, rFSH+rLH has a superior effect on embryo quality and ongoing pregnancy than rFSH alone in obese or overweight patients without PCOS. In addition, it is seen that the endometrium of these patients on the hCG day is thicker when rFSH+rLH is used than when HP-HMG is used.

Ethics Committee Approval: The study was approved by Kocaeli University Ethics Committee (Project number: 2021/295).This research was conducted in accordance with the ethical stansdards of the Helsinki declaration and its later amendments..

Author Contributions: MD, OSYC, ED and BV designed the study. MD, ES, SD, LY, and OOD collected data. MD, OSYS, ES and ED performed the data analysis and interpreted the analyses. MD, OSYS and LY reviewed the literature. MD, OSYS, ES, LY, SD, OOD, BV and ED critically reviewed the article and made critical revisions. All authors have read and approved the final version of the article.

Conflict of Interest: All of the authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest.

Funding: The study does not have any funding resources.

Informed Consent: Informed consent was not obtained as the study was retrospective.

REFERENCES

1. Agha M, Agha R. The rising prevalence of obesity: part A: impact on public health. Int J Surg Oncol (N Y). 2017;2(7):e17.

2. Dağ ZÖ, Dilbaz B. Impact of obesity on infertility in women. J Turk Ger Gynecol Assoc. 2015;16(2):111-117.

3. Fedorcsák P, Dale PO, Storeng R, et al. Impact of overweight and underweight on assisted reproduction treatment. Hum Reprod. 2004;19(11):2523-2528.

4. Supramaniam PR, Mittal M, McVeigh E, Lim LN. The correlation between raised body mass index and assisted reproductive treatment outcomes: a systematic review and meta-analysis of the evidence. Reprod Health. 2018;15(1):34.

5. Blank SK, McCartney CR, Marshall JC. The origins and sequelae of abnormal neuroendocrine function in polycystic ovary syndrome. Hum Reprod Update. 2006;12(4):351-361.

6. Catteau A, Caillon H, Barrière P, Denis MG, Masson D, Fréour T. Leptin and its potential interest in assisted reproduction cycles. Hum Reprod Update. 2016;22(3):320-341.

7. Tortoriello DV, McMinn J, Chua SC. Dietary-induced obesity and hypothalamic infertility in female DBA/2J mice. Endocrinology. 2004;145(3):1238-1247.

8. Vural F, Vural B, Çakıroğlu Y. The Role of Overweight and Obesity in In Vitro Fertilization Outcomes of Poor Ovarian Responders. Biomed Res Int. 2015;2015:781543.

9. Vural F, Vural B, Çakiroglu Y. In vitro fertilization outcomes in obese women under and above 35 years of age. Clin Exp Obstet Gynecol. 2016;43(2):233-237.

10. Vuong TN, Phung HT, Ho MT. Recombinant follicle-stimulating hormone and recombinant luteinizing hormone versus recombinant follicle-stimulating hormone alone during GnRH antagonist ovarian stimulation in patients aged ≥35 years: a randomized controlled trial. Hum Reprod. 2015;30(5):1188-1195.

11. Demir M, Sertel E, Cicek OSY, Yalcınkaya L, Dogan S, Daloglu OO et al. The Effect of Recombinant LH Addition to Recombinant FSH on Assisted Reproductive Technologies Outcomes in Overweight and Obese Patients without Polycystic Ovary Syndrome. OJOG. 2020; 10, 433-444.

12. Tayyar AT, Kahraman S. Comparison between cycles of the same patients when using recombinant luteinizing hormone + recombinant follicle stimulating hormone (rFSH), human menopausal gonadotropin + rFSH and rFSH only. Arch Med Sci. 2019 May;15(3):673-679.

13. Orvieto R. HMG versus recombinant FSH plus recombinant LH in ovarian stimulation for IVF: does the source of LH preparation matter?. Reprod Biomed Online. 2019;39(6):1001-1006.

14. Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod. 2004;19(1):41-47.

15. Blank C, DeCroo I, Weyers B, et al. Improvement instead of stability in embryo quality between day 3-5: A possible extra predictor for blastocyst selection. Eur J Obstet Gynecol Reprod Biol. 2020;253:198-205.

16. Alpha Scientists in Reproductive Medicine and ESHRE Special Interest Group of Embryology. The Istanbul consensus workshop on embryo assessment: proceedings of an expert meeting. Hum Reprod. 2011;26(6):1270-1283.

17. Gardner DK, Schoolcraft WB. Culture and transfer of human blastocysts. Curr Opin Obstet Gynecol. 1999;11(3):307-311.

18. Van den Abbeel E, Balaban B, Ziebe S, et al. Association between blastocyst morphology and outcome of single-blastocyst transfer. Reprod Biomed Online. 2013;27(4):353-361.

19. Blank C, Wildeboer RR, DeCroo I, et al. Prediction of implantation after blastocyst transfer in in vitro fertilization: a machine-learning perspective. Fertil Steril. 2019;111(2):318-326.

20. Pacchiarotti A, Sbracia M, Frega A, Selman H, Rinaldi L, Pacchiarotti A. Urinary hMG (Meropur) versus recombinant FSH plus recombinant LH (Pergoveris) in IVF: a multicenter, prospective, randomized controlled trial. Fertil Steril. 2010;94(6):2467-2469.

21. Tesarik J, Mendoza C. Effects of exogenous LH administration during ovarian stimulation of pituitary down-regulated young oocyte donors on oocyte yield and developmental competence. Hum Reprod. 2002;17(12):3129-3137.

22. Balasch J, Miró F, Burzaco I, et al. The role of luteinizing hormone in human follicle development and oocyte fertility: evidence from in-vitro fertilization in a woman with long-standing hypogonadotrophic hypogonadism and using recombinant human follicle stimulating hormone. Hum Reprod. 1995;10(7):1678-1683.

23. Bühler KF, Fischer R. Recombinant human LH supplementation versus supplementation with urinary hCG-based LH activity during controlled ovarian stimulation in the long GnRH-agonist protocol: a matched case-control study. Gynecol Endocrinol. 2012;28(5):345-350.

24. Shahrokh Tehraninejad E, Farshbaf Taghinejad M, Hossein Rashidi B, Haghollahi F. Controlled ovarian stimulation with r-FSH plus r-LH vs. HMG plus r-FSH in patients candidate for IVF/ICSI cycles: An RCT. Int J Reprod Biomed. 2017;15(7):435-440.

25. Requena A, Cruz M, Ruiz FJ, García-Velasco JA. Endocrine profile following stimulation with recombinant follicle stimulating hormone and luteinizing hormone versus highly purified human menopausal gonadotropin. Reprod Biol Endocrinol. 2014;12:10.

26. Mignini Renzini M, Brigante C, Coticchio G, et al. Retrospective analysis of treatments with recombinant FSH and recombinant LH versus human menopausal gonadotropin in women with reduced ovarian reserve. J Assist Reprod Genet. 2017;34(12):1645-1651.

27. Revelli A, Pettinau G, Basso G, et al. Controlled Ovarian Stimulation with recombinant-FSH plus recombinant-LH vs. human Menopausal Gonadotropin based on the number of retrieved oocytes: results from a routine clinical practice in a real-life population. Reprod Biol Endocrinol. 2015;13:77.

28. Xia X, Shi Y, Geng L, et al. A cohort study of both human menopausal gonadotropin (HMG) and recombinant luteinizing hormone addition at early follicular stage in in vitro fertilization outcome: A STROBE-compliant study. Medicine (Baltimore). 2019;98(19):e15512.

29. Lv H, Li X, Du J, et al. Effect of endometrial thickness and embryo quality on live-birth rate of fresh IVF/ICSI cycles: a retrospective cohort study. Reprod Biol Endocrinol. 2020;18(1):89.