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Comparing rLH with hMG in embryo transfers at the stage of blastocyst and pregnancy outcomes in poor responders

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Abstract

Despite showing the beneficial effects of adding LH activity to FSH, based on the pregnancy rate (PR) in patients in the previous studies, no studies have been done to compare two different gonadotrophin preparations with activity of LH in the same group of poor responders. The present study was a single-center retrospective one conducted in January 2015 - December 2019 among 30 women under 39 years old who had reduced ovarian reserve and underwent ICSI cycles. The same patient group received rFSH combined with hMG or rLH. The ovarian stimulation cycle began on the second day of the menstrual cycle, and the initial doses of gonadotrophin were 225 IU/day rFSH in addition to 75 IU/day hMG or 75 IU/day rLH. In all cycles, a flexible antagonist protocol was used. Adding rLH significantly increased the mean number of MII oocytes and cumulus oophorus complex (COC) ($p < 0.001$). There was no significant difference between poor responders treated with rLH or with hMG in terms of blastocyst transfer, implantation rates and clinical pregnancy rates ($p>0.05$). There should be further studies to confirm the better effect of rLH addition to rFSH than hMG in young poor responders. Interventions for poor responders obviously need large, randomized studies which were designed properly, due to the lack of evidence-based treatment to date for this particular patient group.

Keywords: hMG, poor responder, rLH, rFSH

1. Introduction

Poor ovarian response (POR) occurs in 9-24% of IVF cycles. Roughly 80% of the IVF cycle cancelations in the U.S. occur due to the inability to obtain sufficient oocytes. Pregnancy rates (PRs) in poor responders vary from 14-34.5% (1). As is generally known, controlled ovarian stimulation (COS) is used to get enough quality oocytes to reach pregnancy (2). Although a poor response to ovarian stimulation creates difficulties in IVF practices, many new treatment strategies are being developed (3), one of which is the use of luteinizing hormone (LH) in assisted reproductive technology (ART) cycles (4). LH is effective in gonadal functions and is also involved in follicle growth and ovulation, exerting a synergistic effect with follicle stimulating hormone (FSH). LH has been shown to reduce cumulus cell apoptosis and cause an increase in oocyte maturity and quality (5). The developing follicles theca cells are also induced by LH to produce growth factors of androgens and polypeptide, enhancing the follicular response to FSH during follicular selection and recruitment (6). ART is therefore used during the LH hormone cycle for difficult patients with diminished ovarian reserve, advanced maternal age, and a lower chance of success. However, there are uncertainties in the literature on the use of LH, and there is no consensus regarding the patients for whom it should be used, during which cycle it should be started, or whether urinary or recombinant preparations should be used (7). Two sources of exogenous LH activity are used in the IVF cycles, rLH and human menopausal gonadotropin (hMG), the latter of which has both LH and FSH activity (7, 8). There are many studies in the literature comparing the effects of these two different LH preparations (9, 10); however, the patient heterogeneity in these studies is extremely high. Therefore, in the present study, to reduce the patient heterogeneity, we aimed to compare rLH and hMG cycles performed in the same poor responder patients during the same year.

2. Materials and methods

2.1. Participants

A total of 30 patients were included, all which cycles were performed in the Department of Assisted Reproductive Technologies and Reproductive Genetics, BAU Medical Park Göztepe Hospital, Turkey, between 2015 and 2019. The procedures were done in accordance with the regulations established by the Clinical Research and Ethics Committee

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and the Helsinki Declaration of World Medical Association. The study was carried out with the permission of the Local Institutional Review Board and Istanbul Medeniyet University Göztepe Research and Training Hospital (Permission granted/CAAE number. 2020, Decision no: 0669). Signed informed consents were obtained from all patients. Women who had a BMI of 18-30 kg/m^2, were eligible for IVF, ≥ 18 and < 39 years old, and were diagnosed with POR based on the 2011 ESHRE Bologna criteria were included in the present study. As the Bologna criteria showed, there should be at least two of the following three features: (a) an abnormal ovarian reserve test (i.e., AMH, 0.5-1.1 ng/mL or AFC, 5-7 follicles), (b) a previous POR (≤3 oocytes with a conventional stimulation protocol), and (c) advanced maternal age (≥ 40 years) or any other POR risk factor, (11). Those diagnosed with tubal pathologies, uterine anomalies, grade 3-4 endometriosis, or those with any lesion in the uterus were excluded from the study. The collected data included BMI (kg/m^2), age, FSH levels on cycle day 2, total dosage of gonadotropins, anti-Mullerian hormone (AMH), number of previous ART attempts, total number of oocytes retrieved, duration of stimulation, number of embryo transfers performed, total number of mature oocytes, peak estradiol level and endometrial thickness values, blastocyst formation ratio, implantation rates and clinical pregnancy rates.

2.2. Assisted reproduction procedures

Controlled ovarian stimulation (COS) was started on the second day of cycle in all patients. The starting gonadotrophin doses were 225 IU/day rFSH in addition to75 IU/day u-hMG or 75 IU/day rLH. For all cycles, the flexible antagonist protocol was used. When a minimum of two follicles achieved a mean diameter of > 17 mm, a single dose of 250 µg rec hCG (Ovitrelle amp 250 µg/0.5 mL, Merck-Serono, Istanbul, Turkey) or 10,000 IU urinary hCG (Pregnyl amp 5000 IU, Organon, Istanbul, Turkey) was administered. Oocyte retrieval guided by the transvaginal US, was performed 35-36 hours after the administration of rhCG. Standard intracytoplasmic sperm injection techniques were utilized to fertilize the oocytes. All frozen-thawed embryo transfers were performed by same highly experienced clinician, using the Wallace catheter with the after-load transfer technique guided by the transabdominal US and without using any sedation or anesthesia. The embryos with the best quality based on their morphology were selected for transfer. Based on the quality and number of the existing embryos, indication for IVF, and maternal age, there was transfer of one or two embryos on the fifth day. Daily vaginal progesterone gel (Crinone 8%, 90 mg; Merck Serono, Central Pharma Ltd, Bedfordshire, UK) was implemented as luteal-phase support.12 days after ET, serum quantitative β-hCG levels were obtained. A clinical pregnancy means that there is a gestational sac visualized through transvaginal US examination.

2.3. Statistical analysis

For statistical analysis, SPSS 15.0 for Windows was used. Descriptive statistics including the minimum, and maximum for numerical variables, standard deviation, mean, and percentages and numbers of categorical variables was given. dependent groups were compared using a paired sample t-test when the normal distribution conditions differences were met by the numerical variables, and the Wilcoxon test was used when the normal distribution conditions were not met. The difference between the dependent groups in the rates was examined through McNemar analysis. The statistical significance level was accepted as p> 0.05.

3. Results

In total, 30 patients with a mean age of 31.5±4.8 years were included in the present study. The mean BMI value was 24.3±3.9, the mean AMH value was 0.81±0.26, and the mean D3 FSH was 8.46±3.9/(4-11). The demographic characteristics of the patients are given in Table 1.

Table 1. The patients' demographic characteristics

	Mean ± SD/(min−max) (n = 30)
Female age (years)	31.5 ± 4.8/ (21-38)
Male age (years)	36.2 ± 4.1/ (27-42)
BMI (kg/m²)	24.3 ± 3.9/ (18-30)
AMH (ng/mL)	0.81 ± 0.26/ (0.23-1)
D3 FSH (mIU/mL)	8.46 ± 3.9/ (4-11)

AMH, anti-Mullerian hormone; FSH; follicle-stimulating hormone; BMI; body mass index

The treatment results for rLH and hMG that patients received in the same year are summarized in Table 2. In the rLH treatment group, total number of retrieved oocytes, and mean number of MII oocytes were statistically significantly higher compared to those in the hMG treatment (p = 0.001, p=0.003). The rate of blastocyst formation was 70% in patients using rLH and 53.3% in patients using hMG. No statistically significant difference was found regarding blastocyst formation during the treatment period (p=0.289, p=0.302). Also, there was no statistical significance for implantation rates and clinical pregnancy rates between two groups. (p = 0.137, p= 0.269).

4. Discussion

To date, no existing study proves the superiority of any gonadotropin used during COS in poor responder patients. Although many studies have been conducted on this subject, the heterogeneous and variable patient groups have produced contradictory results. The present study aimed to eliminate the variables. Therefore, we compared different cycles used hMG or rLH in the same patient group. We also compared the blastocyst formation rate and clinical pregnancy rate of both groups using rLH or hMG supplementation from the beginning of early follicular phase. Our study shows no significant difference in blastocyst formation or clinical rates of pregnancy following the addition of either hMG or rLH to rFSH.

Table 2. Clinical characteristics of the patients

		rLH	hMG	
		Mean ± SD/median (n = 30)	Mean ± SD/median (n = 30)	*p*
Previous IVF attempts		1.70 ± 1.49/1	1.63 ± 0.93/2	0.736
Total GND dose (IU)		2545.8 ± 356.7/2550	2542.5 ± 579.4/2362.5	0.959
Total stimulation days		9.20 ± 0.41/9	9.13 ± 0.35/9	0.480
Total retrieved oocytes		5.17 ± 2.36/5	4.17 ± 1.82/4	**0.001**
MII oocytes		4.03 ± 1.75/3	3.37 ± 1.35/3	**0.003**
PN		3.50 ± 1.70/3	3.17 ± 1.26/3	0.115
Estradiol on hCG day		715.8 ± 347.2/592.5	697.3 ± 352.8/467	0.848
Endometrial thickness		10.04 ± 1.27/9.95	9.83 ± 1.28/9.45	0.539
		n (%)	n (%)	*p*
Number of blastocysts	**N**o	9 (30.0)	14 (46.7)	0.302
	Yes	21 (70.0)	16 (53.3)	
Number of embryos transferred	**1**	24 (80.0)	26 (86.7)	0.625
	2	6 (20.0)	4 (13.3)	
Implantation rate (%)		17.1	15.2	0.137
Clinical pregnancy rate (%)		22.3	19.7	0.269

FSH: follicle-stimulating hormone; GND: gonadotropin; PN: pronucleu

Despite certain studies indicating the positive effects of rLH supplementation on the pregnancy rates of specific populations with diminished ovarian reserve, low serum LH levels, or an advanced age (12-14), the 2017 meta-analysis performed by Mochtar et al. found no difference between the live birth rates of women using rFSH alone and in combination with rLH. In another meta-analysis, however, a small RCT conducted among poor responders demonstrated a positive effect of pretreatment with rLH on the live birth rate (15). Nevertheless, a more recent, larger RCT showed no benefit to rLH addition for the clinical pregnancy rate of Bologna-classified poor responders (16). Also, in the present study, a clinical pregnancy rates were similar between two groups.

Although studies on hMG use in poor responders are more limited, a pilot study conducted by Polyzos et al. showed that hMG use in patients under the age of 40 increases the ongoing pregnancy rate and that the use of hMG is promising in the case of poor responders (17, 18). In the newest RCT, Drakopoulos et al. reported that hMG use in 152 poor responders, classified based on the Bologna criteria, did not change their pregnancy rate as compared to the group using only rFSH. In this study, the clinical pregnancy rate was found to be 14.3% in the hMG group and 17.1% in the rFSH group. Similarly, in our study, the clinical pregnancy rate was lower in the hMG group (19.7%) but it was not significant. Although no studies in the existing literature compare the use of rLH and hMG in poor responders, as classified based on the Bologna criteria, there are existing studies that compare two different LH sources. In a study on 4719 patients cured with a GnRH agonist protocol, Buhler and Fischer found higher clinical pregnancy rate in the rLH group than that in the hMG group (25.5% vs. 21.7%, respectively) (3). A retrospective study conducted by Dahan et al. showed the addition of rLH for the patients treated with a serum FSH level of > 10 IU/L to be more effective toward raising clinical rates of pregnancy than the addition of hMG (5). It was found that the number of oocytes in this study was significantly higher in the rLH group than in the hMG group. In accordance, the number of MII oocytes and retrieved oocytes in the present study was significantly higher in the rLH group (p=0.003, p=0.001). This effect may have resulted from the cAMP- and protein kinase-mediated proapoptotic effects of hCG in granulosa cells (19). A possible cause of the higher pregnancy rates in patients using rLH may be the longer half-life of hCG. This prolonged effect had a negative impact on the endometrium in terms of luteinizing hormone-chorionic gonadotropin receptor (LHCGR) downregulation (20, 21). Since we performed frozen embryo transfers in the present study, we did not see this effect, and we determined that there was a similar pregnancy rate in both groups. We applied rLH- and hMG-induced LH supplementation to poor responders classified based on the Bologna criteria. The advantage of this study was that both treatments were applied to the same patient group, which eliminated patient heterogeneity. Despite the higher number of MII oocytes and retrieved oocytes in the rLH group, the clinical pregnancy or blastocyst formation rates had no statistically significant difference. Further studies will confirm whether the addition of rLH increases higher pregnancy rate as compared to the addition of hMG in young poor responders. To achieve this, large and professionally designed randomized studies are required, since there is no evidence-based treatment to date for poor responders.is no evidence-based treatment to date for poor responders.

Conflict of interest

Authors declare that there is no conflict of interest.

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References

1. Blumenfeld Z. What is the best regimen for ovarian stimulation of poor responders in ART/IVYF. Front Endocrinol (Lausanne). 2020; 11:192.
2. Bosch E, Labarta E, Crespo J, Simon C,Remohi J,Pellicer A.Impact of luteinizing hormone administration on gonadotropin-releasing hormone antagonist cycles: an age-adjusted analysis. Fertil Steril. 2011; 95(3):1031-1036.
3. Buhler 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.
4. Casarini L, Santi D, Brigante G, Simoni M. Two hormones for one receptor: evolution, biochemistry, actions, and pathophysiology of LH and hCG. Endocr Rev. 2018; 39(5):549-592.
5. Dahan MH, Agdi M, Shehata F, Son W,Tan S. A comparison of outcomes from in vitro fertilization cycles stimulated with either recombinant luteinizing hormone (LH) or human chorionic gonadotropin acting as an LH analogue delivered as human menopausal gonadotropins, in subjects with good or poor ovarian reserve: a retrospective analysis. Eur J Obstet Gynecol Reprod Biol. 2014 Jan; 172:70-73.
6. Drakopoulos P, Vuong TNL, Ho NAV, Vaiarelli A,Ho MT,Blockeel C,et al. Corifollitropin alfa followed by highly purified HMG versus recombinant FSH in young poor ovarian responders: a multicentre randomized controlled clinical trial. Hum Reprod. 2017; 32(11):2225-2233.
7. Ferraretti AP, La Marca A, Fauser BC,Tarlatzis B,Nargund G.Gianoroli L. ESHRE consensus on the definition of 'poor response' to ovarian stimulation for in vitro fertilization: the Bologna criteria. Hum Reprod. 2011; 26(7):1616-1624.
8. Ferraretti AP, Gianaroli L, Motrenko T, Feliciani E,Tabanelli C,Magli MC. LH pretreatment as a novel strategy for poor responders. Biomed Res Int. 2014; 2014:926172.
9. Hill MJ, Levens ED, Levy G, Ryan M,Csokmay JM,DeCherney AH,Whitcomb BW.The use of recombinant luteinizing hormone in patients undergoing assisted reproductive techniques with advanced reproductive age: a systematic review and meta-analysis. Fertil Steril. 2012; 97(5):1108-1114.
10. Humaidan P, Chin W, Rogoff D,Hoohhe TD,Longobardi S,Hubbard J et al. Efficacy and safety of follitropin alfa/lutropin alfa in ART: a randomized controlled trial in poor ovarian responders. Hum Reprod. 2017 ;32(3):544-555.
11. Kolibianakis EM, Venetis CA, Diedrich K,Tarlatzis BC,Griesinger G. Addition of growth hormone to gonadotrophins in ovarian stimulation of poor responders treated by in-vitro fertilization: a systematic review and meta-analysis. Hum Reprod Update. 2009 (6):613-622.
12. Kyrou D, Kolibianakis EM, Venetis CA, Papanicolaou G,Bontis Bontis J,Tarlatzis BC.How to improve the probability of pregnancy in poor responders undergoing *in vitro* fertilization: a systematic review and meta-analysis. Fertil Steril. 2009; (3):749-766.
13. Lehert P, Kolibianakis EM, Venetis CA,Schertz J,Saunders H,Arriagada P, et al. Recombinant human follicle-stimulating hormone (r-hFSH) plus recombinant luteinizing hormone versus r-hFSH alone for ovarian stimulation during assisted reproductive technology: systematic review and meta-analysis. Reprod Biol Endocrinol. 2014; 20;12:17.
14. Levi Setti PE, Alviggi C, Colombo GL,Pisanelli C,Ripellino C,Longobardi S.,et al. Human recombinant follicle stimulating hormone (rFSH) compared to urinary human menopausal gonadotropin (HMG) for ovarian stimulation in assisted reproduction: a literature review and cost evaluation. J Endocrinol Invest. 2015; 38(5):497-503.
15. Mochtar MH, Danhof NA, Ayeleke RO,Veen FV,Welly M.Recombinant luteinizing hormone (rLH) and recombinant follicle stimulating hormone (rFSH) for ovarian stimulation in IVF/ICSI cycles. Cochrane Database Syst Rev. 2017; 5(5):CD005070.
16. Oudendijk JF, Yarde F, Eijkemans MJ, Broekmans FJM, Brooer SL. The poor responder in IVF: is the prognosis always poor?: a systematic review. Hum Reprod Update. 2012; 18(1):1-11.
17. Polyzos NP, De Vos M, Corona R, Vloeberghs V, Ortega-Hrepich C, Stoop D, et al. Addition of highly purified HMG after corifollitropin alfa in antagonist-treated poor ovarian responders: a pilot study. Hum Reprod. 2013; 28(5):1254-1260.
18. Revelli A, Chiado' A, Guidetti D, Bongioanni F, Rovei V, Gennarelli G. Outcome of in vitro fertilization in patients with proven poor ovarian responsiveness after early vs. mid-follicular LH exposure: a prospective, randomized, controlled study. J Assist Reprod Genet. 2012 Sep; 29(9):869-875.
19. Revelli A, Pettinau G, Basso G, Carosso A, Ferrero A, Dallan C, 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 Jul 25;13:77.
20. Ruvolo G, Bosco L, Pane A, Morici G, Cittadini E, Roccheri MC. Lower apoptosis rate in human cumulus cells after administration of recombinant luteinizing hormone to women undergoing ovarian stimulation for in vitro fertilization procedures. Fertil Steril. 2007; 87(3):542-546.
21. 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;15(3):673-679.
22. Zhang Y, Zhang C, Shu J, Guo J, Chang HM, Leung PCK, et al. Adjuvant treatment strategies in ovarian stimulation for poor responders undergoing IVF: a systematic review and network meta-analysis. Hum Reprod Update. 2020; 26(2):247-263.