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Comparing highly purified human menopausal gonadotropin and recombinant follicle stimulating hormone in poor ovarian reserve patients undergoing intracytoplasmic sperm injection

Srovnání vysoce purifikovaného lidského menopauzálního gonadotropinu a rekombinantního folikulostimulačního hormonu u pacientek s nedostatečnou ovariální rezervou podstupujících intracytoplazmatickou injekci spermie

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Summary: Objective: We aimed to compare highly purified human menopausal gonadotropin (hp-hMG) and recombinant follicle stimulating hormone (rFSH) in short antagonist *in vitro* fertilization (IVF) cycles of patients with poor ovarian reserve (POR). Limited research exists on this comparison in short antagonist cycles for this patient group. **Materials and methods:** This retrospective cohort study involved 165 POR patients aged 18–45 years who underwent IVF between 2018 and 2022. Patients were divided into two groups based on their GnRH antagonist protocol: hp-hMG (group 1 = 72) and rFSH (group 2 = 93). We compared pregnancy outcomes, number of oocytes collected, mature oocytes retrieved, mean fertilized oocytes, top quality embryos transferred, and serum estradiol (E2) and progesterone (P) levels on human chorionic gonadotropin (hCG) administration day. **Results:** No significant differences were found in E2 and P levels on hCG trigger day, endometrial thickness on transfer day, stimulation duration, total oocyte number, and mature oocyte number ($P > 0.05$). The total gonadotropin dose was significantly higher in the rFSH group ($P < 0.001$). The number of top-quality embryos transferred and clinical pregnancy and live birth rates did not differ significantly between groups ($P = 0.320$; $P = 0.310$; $P = 0.652$; and $P = 0.662$, resp.)**. Conclusion:** Neither hp-hMG nor rFSH showed superiority in patients with POR, indicating similar effectiveness in this population.

Key words: highly purified human menopausal gonadotropin – *in vitro* fertilization – live birth – poor ovarian reserve – recombinant follicle stimulating hormone

Introduction

Patients undergoing assisted reproductive technologies (ART) are heterogeneous in their response to gonadotropin stimulation. Infertile patients with a diminished ovarian reserve, referred to as poor ovarian responders, are estimated to happen in 10–25% of assisted reproduction patients and the estimated live birth rate in poor ovarian reserve (POR) patients is less than 10%, regardless of ovarian stimulation parameters and age [1]. For these reasons, ART outcomes for POR patients remain a great challenge, and choosing a suitable treatment protocol for these patients is essential. Bologna criteria developed by the European Society of Human Reproduction and Embryology is used to identify patients with low ovarian reserve [2]. They must possess at least two of the three following features:

Souhrn: Cíl: Zaměřili jsme se na srovnání vysoce purifikovaný lidský menopauzální gonadotropin (hp-hMG) a rekombinantní folikuly stimulující hormon (rFSH) v krátkých antagonistických cyklech *in vitro* fertilizace (IVF) u pacientek se špatnou ovariální rezervou (POR). Pro tuto skupinu pacientek existuje omezený výzkum tohoto srovnání v krátkých cyklech antagonistů. **Materiály a metody:** Tato retrospektivní kohortová studie zahrnovala 165 pacientek s POR ve věku 18–45 let, kteří podstoupili IVF v letech 2018–2022. Pacienti byli rozděleni do dvou skupin na základě protokolu s antagonistou GnRH: hp-hMG (skupina 1 = 72) a rFSH (skupina 2 = 93). Porovnávali jsme výsledky těhotenství, počet odebraných oocytů, odebrané zralé oocyty, průměrný počet oplodněných oocytů, transferovaná embrya nejvyšší kvality a hladiny sérového estradiolu (E2) a progesteronu (P) v den podání hCG. **Výsledky:** Nebyly nalezeny žádné signifikantní rozdíly v hladinách E2 a P v den spouštění hCG, tloušťce endometria v den přenosu, délce stimulace, celkovém počtu oocytů a počtu zralých oocytů ($p > 0,05$). Celková dávka gonadotropinu byla významně vyšší ve skupině s rFSH ($p < 0,001$). Počet transferovaných embryí špičkové kvality a klinické těhotenství a porodnost se mezi skupinami významně nelišily ($p = 0,320$; $p = 0,310$; $p = 0,652$ a $p = 0,662$). **Závěr:** Ani hp-hMG ani rFSH neprokázaly převahu u pacientek s POR, což ukazuje na podobnou účinnost v této populaci.

Klíčová slova: vysoce purifikovaný lidský menopauzální gonadotropin – *in vitro* fertilizace – živě narozené děti – špatná ovariální rezerva – rekombinantní folikuly stimulující hormon

- age ≥ 40 years or with other risk factors for POR;
- ≤ 3 oocytes retrieved from the previous *in vitro* fertilization/intra-cytoplasmic sperm injection (IVF/ICSI) cycle using a conventional stimulation protocol;
- antral follicle count < 7 or Anti-Müllerian hormone (AMH) < 1.1 ng/mL.

Making individual treatments for the patient increases our success. However, there is insufficient evidence about which gonadotropin type and at which dose treatments improve pregnancy rates in patients with POR [2]. Highly purified human menopausal gonadotropin (hp-hMG) and recombinant follicle stimulating hormone (rFSH) have been used for controlled ovarian stimulation (COS) during ICSI separately or in combinations. Their effects on cycle characteristics and pregnancy outcomes have been discussed in many studies. De Placido et al. suggested rFSH is effective in patients with low ovarian reserve [3]. Another study evaluated the clinical outcomes of using hp-hMG versus rFSH in the first treatment cycle of IVF or ICSI. It found similar pregnancy and live birth rates between the two groups, but noted that cycles with rFSH were characterized by shorter stimulation durations, lower gonadotrophin consumption, and an increased number of oocytes and embryos [4]. Adding luteinizing hormone (LH) in IVF cycles can be particularly important in specific patient groups. LH supports follicular development, oocyte maturation, and progesterone production, thereby aiding in a better ovarian response and improved embryo quality [5]. One meta-analysis revealed that the co-treatment of rFSH with recombinat LH (rLH) can lead to better clinical outcomes in women over 35 undergoing fresh IVF cycles, suggesting an improvement in clinical pregnancy rates and the number of mature oocytes retrieved [6]. Another study supported these findings, highlighting that rLH supplementation can significantly increase clinical pregnancy rates and the number of oocytes retrieved in women who initially respond poorly to rFSH [7].

We aimed to compare cycle parameters and pregnancy outcomes in patients with POR undergoing short antagonist IVF cycles using rFSH or hp-hMG. This study is one of the few that compares cycle parameters and pregnancy outcomes between rFSH and hp-hMG in patients with POR receiving a short antagonist IVF protocol.

Materials and methods

Design and setting

This retrospective cohort study was conducted between 2018 and 2022 at the University of Health Sciences Konya City Hospital IVF unit after receiving approval from the Institutional Review Board of the University of Health Sciences protocol number 12–51 on 7. 12. 2023. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All patients consented to participate in the study.

Patient population and inclusion-exclusion criteria

Patients with polycystic ovary syndrome, male factor infertility, tubal factor, endometriosis, unexplained infertility, hypogonadotropic hypogonadism, body mass index > 30 kg/m^2, and patients with systemic diseases were not included in the study. Only patients with poor ovarian reserve who met the Bologna criteria were included in the study.

Study protocol

Total of 165 IVF patients with poor ovarian reserve were included in this study; 72 received hp-hMG (Menopur; Ferring, Sweden) (group 1) and 93 received rFSH (Gonal F; Serono, Geneva, Switzerland) (group 2) for COS during ICSI with the GnRH antagonist protocol. We decided which type of gonadotropin to start on each individual patient, based on the economic situation of the patients and the increase in the dollar exchange rate in our country during the pandemic period, as well as the drugs available in pharmacies' stocks. Pregnancy-related outcomes (clinical pregnancy and live birth rate), number of collected oocytes, number of mature

oocytes (M2), number of fertilized oocytes, number of transfered embryos, embryo grades (grade 1–3), and serum E2 and progesterone levels on the day of hCG administration parameters were compared between the two groups.

Basal hormone profiles were examined in all patients on the second day of menstruation. After persistent follicular cysts are excluded by transvaginal ultrasound, 300 IU/day (subcutaneously (SQ) as the initial dose of hp-hMG (Menopur; Ferring, Istanbul) or rFSH (Gonal F; Merck, Istanbul) was started in the patients. GnRH antagonist cetrorelix (Cetrotide; Merck, Istanbul) was administered daily at 0.25 mg when follicle size reached 12–13 mm in both groups and continued until the end of stimulation. When follicle size reached 18 mm, rec hCG (Ovitrelle; Merck, Istanbul) injection was performed and oocytes were collected after 36 hours. Under ultrasound guidance, one or two embryos were transferred on day 3 of the cleavage stage. Standard luteal support was administered with 600 mg/day vaginal micronized progesterone (Progestan, Koçak Farma, Istanbul). Twelve days after embryo transfer, patients were called in for a check-up for a pregnancy test. Clinical pregnancy was defined as the presence of a fetal heartbeat on ultrasonography performed 4–5 weeks later in patients with a positive pregnancy test, births at 24 weeks, or over 500 grams were considered live births.

Statistical analysis

Statistical Package for the Social Sciences version 22.0 (SPSS, IBM Corp., Armonk, NY, USA) was used to perform statistical analyses on the research data. The Kolmogorov-Smirnov test was used to check for data normality. Categorical variables were expressed as number (N) and percentage (%), while continuous variables were reported as the median (25^{th}–75^{th} percentile). Continuous variables were evaluated with the Mann-Whitney U-Test. The Pearson Chi-square Test was used to compare categorical data. Statistical significance was assumed to be at the $P < 0.05$ level.

Tab. 1. Demographic and baseline characteristics of the patients.
Tab. 1. Demografické a výchozí charakteristiky pacientek.

Baseline characteristics	Group hp-hMG, N = 72	Group rFSH, N = 93	P-value
year	36 (33–39)	37 (35–39)	0.431
BMI (kg/m^2)	25 (23–27)	25 (23–28)	0.478
AFC	5 (3–6)	4 (3–6)	0.830
FSH (IU/mL)	9 (7–12)	9 (7–11)	0.884
LH (IU/mL)	9 (6–10)	7 (5–9)	**0.001**
basal E2 (pg/mL)	45 (34–57)	45 (35–55)	0.774
AMH (ng/mL)	0.6 (0.2–1)	0.5 (0.1–1)	0.478

Variables are presented as median (25^{th}–75^{th} percentiles). Mann-Whitney U-Test was used. AFC – antral follicle count, AMH – Anti-Müllerian hormone, BMI – body mass index, E2 – estradiol, FSH – follicle-stimulating hormone, hp-hMG – high purified human menopausal gonadotropin, LH – luteinizing hormone, N – number, rFSH – recombinant follicle stimulating hormone

Results

This retrospective study included 165 IVF patients; 93 were administered rFSH for COS during ICSI using the GnRH antagonist protocol, while 72 were administered hp-hMG. Patients in the groups had similar characteristics in terms of age, BMI (body mass index), antral follicle count (AFC), follicle stimulating hormone (FSH), basal estradiol (E2), and AMH parameters ($P > 0.05$). In addition, LH levels were statistically significantly higher in patients in Group 1 (hp-hMG) ($P = 0.001$) (Tab. 1).

When the ovarian stimulation parameters of the groups were examined, the total gonadotropin dose was higher in the rFSH group, and this difference was found to be statistically significant ($P < 0.001$). In addition, hCG trigger day E2, trigger day P (progesterone), trigger day endometrium thickness, transfer day endometrial thickness, stimulation duration, total oocyte number, and M2 oocyte number parameters were similar in the groups ($P > 0.05$). Total fertilization failure (TFF) was present in 8.3% of the patients in Group hp-hMG and 7.5% in Group rFSH, which is not statistically significant between groups ($P = 0.849$) (Tab. 2).

Considering the pregnancy parameters of the groups, fertilized oocyte numbers and number of transferred embryos were similar in the groups ($P = 0.688$ and $P = 0.421$, resp.). When evaluated in terms of embryo grade, "Grade 1" rate was 32.3% in Group hp-hMG, while it was 23% in Group rFSH; Grade 2 rate was 32.3% in Group hp-hMG, and it was 43.7% in Group rFSH; and Grade 3 embryo rate was 29% in Group hp-hMG and 27.8% in Group rFSH. Although the percentage of Grade 1 embryos was higher in the hp-hMG group, this was not statistically significant. Regarding the embryo grades between groups, it was not statistically significant ($P = 0.310$).

Considering the clinical pregnancy parameter, pregnancy occurred in 22.2% of Group 1, while this rate was 19.4% in Group 2, and there was no significant difference between the groups ($P = 0.652$). Considering the live birth parameter, live birth occurred in 15.2% in Group 1 patients. In comparison, this rate was 12.9% in Group 2, and there was no significant difference between the groups ($P = 0.662$). Abortion rates were also similar between groups; in Group 1, 31.3% of patients experienced abortion, and in Group 2, this rate was 31.3% ($P = 0.897$) (Tab. 3).

Tab. 2. Ovarian stimulation parameters of the groups.
Tab. 2. Parametry ovariální stimulace skupin.

Parameter	Group hp-hMG, N = 72	Group rFSH, N = 93	P-value
total dose of gonadotropin (IU)	2,563 (2,250–3,000)	3,100 (2,900–3,400)	**< 0.001**
day of Hcg trigger estradiol (pg/mL)	868 (650–1,025)	975 (743–1,100)	0.077
progesterone (ng/mL)	0.9 (0.75–1.1)	1 (0.8–1.1)	0.076
endometrial thickness on Hcg trigger day (mm)	10 (8–12)	9.5 (9–11)	0.383
endometrial thickness on embriyo transfer day (mm)	11 (9–12)	11 (9–12)	0.601
duration of stimulation (day)	10 (9–11)	10 (9–12)	0.252
total oocyte number	4 (2–6)	4 (2–5)	0.792
M2 oocyte number	2 (1–4)	2 (1–3)	0.320
TFF	6 (8.3%)	7 (7.5%)	0.849

Variables are presented as median (25^{th}–75^{th} percentiles). Chi-square Test was applied for categorical variables, while the Mann-Whitney U-Test was used for continuous variables. E2 – estradiol, Hcg – human chorionic gonadotropin, hp-hMG – high purified human menopausal gonadotropin, M2 – mature oocyte, N – number, P – ng/mL, rFSH – recombinant follicle stimulating hormone, TFF – total fertilization failure

Tab. 3. Pregnancy parameters of the groups.
Tab. 3. Těhotenské parametry skupin.

Parameter		Group hp-hMG, N = 72	Group rFSH, N = 93	P-value
number of embryo development		2 (1–2)	1 (1–2)	0.688
number of transferred embryos		1 (1–2)	1 (1–2)	0.421
embryo grade	G1	30 (32.3%)	29 (23%)	0.310
	G2	30 (32.3%)	55 (43.7%)	
	G3	27 (29%)	35 (27.8%)	
clinical pregnancy		16 (22.2%)	18 (19.4%)	0.652
live birth		11 (68.7%)	12 (66.6%)	0.662
abortus		5 (31.3%)	6 (33.3%)	0.897

Variables are presented as median (25^{th}–75^{th} percentiles). Chi-square Test was applied for categorical variables, while the Mann-Whitney U-Test was used for continuous variables. hp-hMG – high purified human menopausal gonadotropin, N – number, rFSH – recombinant follicle stimulating hormone

Discussion

To increase success in IVF cycles, it is important to find the ideal treatment regimen and drug or drug combination while also choosing the lowest-cost route. In this research, we explored which type of gonadotropin could improve cycle features and pregnancy outcomes for patients with POR. We determined that in the IVF cycles of patients with poor ovarian reserve, there was no statistical difference in the hp-hMG or rFSH drug groups in terms of cycle characteristics and pregnancy parameters. But with a statistically significant lower total gonadotropin dose, a similar number of total oocytes, M2 oocytes, and fertilized oocytes were obtained in the hp-hMG patient group as in the rFSH group.

According to ESHRE 2019 guidelines, there is not enough evidence to support any gonadotropin type [8]. Ideal treatment protocol and appropriate drug selection are important in patients with POR, which was the group with the least satisfactory IVF cycle results. Although oocyte donation is the most successful method recommended for this group of patients, oocyte donation is not allowed by our state due to religious problems in our country. Since the main factor determining success in IVF cycles of patients with POR is the number of M2 and high-quality oocytes, many studies have been conducted in the literature regarding drug types and doses to capture this. LH and hCG activity is present in hp-hMG preparations. The belief that LH supplementation increases the number and quality of M2 oocytes is based on the normal physiology of an ovulatory cycle [9]. Although publications compare rFSH and hp-hMG in long agonist and antagonist cycles in different IVF indications, a few articles compare these two drug groups in antagonist cycles with POR patients. This clinical study will contribute to the individualized treatment protocol for POR patients.

In a study published in 2020 by Zhisong Ji et al. [10], they compared rFSH and hp-hMG in the antagonist cycles of 60 patients with POR. There were similar baseline and demographic characteristics of both groups. When we look at the ovarian response and embryo parameters of the two groups, there was no statistical difference in duration of stimulation, total gonadotropin doses or estradiol concentration on hCG day between the groups. Average number of total collected M2 oocytes were (2.90; 2.70; and 2.53 vs. 2.13; 2.30; and 1.80) resp., with $P > 0.005$ for both groups. In addition, they did not find any difference in the groups' pregnancy-related outcomes (clinical pregnancy, implantation rate per transferred embryo, live birth rate). The clinical pregnancy rate for hp-hMG and rFSH was 30.8% vs. 29.4%, resp. In our study, clinical pregnancy and live

birth rates per embryo transfer in the hp-hMG group were 22.2% and 15.2%, while in the rFSH group, they were 19.4% and 12.9%, resp. There was no difference between these pregnancy-related parameters in both groups (P = 0.65 for clinical pregnancy, P = 0.66 for live birth rate per embryo transfer). In our study, the total gonadotropin dose was statistically significantly lower in the hp-hMG group than in the rFSH group (2,563 IU vs. 3,100 IU; P < 0.001). Despite the low total gonadotropin dose in the hp-hMG group, the number of collected oocytes, M2 oocytes, and fertilized oocytes were similar between both groups (4.2 and 2 vs. 4.2.1; P = 0.792; P = 0.320; P = 0.688). Some other studies in the literature investigating the effectiveness of LH reached similar results to ours. In their 2015 study by Vuong et al. [11], which included 240 patients comparing rFSH and rFSH+rLH groups in the antagonist cycles of patients over 35 years of age, they did not find a significant difference in the collected oocyte, live birth, and clinical pregnancy rates when adding rLH to rFSH, similar to our results. The common feature of this study and ours was that the average age groups were similar.

In 2011, among the two groups, Celik et al. [12] applied a long protocol to 87 normal-responder patients and started rFSH or hp-hMG. However, fertilization rates were better in the rFSH group and no significant difference was detected between the groups regarding biochemical, clinical, and ongoing pregnancies.

Contrary to these studies, in some meta-analyses of randomized controlled trials with different IVF indications, statistically higher live birth rates were found in hp-hMG groups compared to rFSH [13,14].

Wu et al. [15] and Kan et al. [16] found better results when adding hp-hMG. Kan et al. added hp-hMG to rFSH on the day of antagonist initiation; they found similar peak estradiol and progesterone levels on hCG trigger day, number of retrieved oocytes and top quality embryo numbers, and fertilization rates between the groups. However, they found that the r-FSH + hp-hMG group had significantly higher implantation rates (35.3% vs. 24.3%; P = 0.017) and clinical pregnancy rates (51.2% vs. 35.8%; P = 0.015). They attributed this result to the implantation-enhancing effect of hCG in hp-hMG. Wu et al. compared three groups in which he did not add any hp-hMG to rFSH with 371 patients in the antagonist cycles of patients with poor ovarian reserve (group 1), added hp-hMG to rFSH with 139 patients in the early follicular period (group 2), and added hp-hMG to rFSH with 172 patients in the late follicular period (group 3); it was determined that adding hp-hMG in the early and late periods increased clinical pregnancy rates. Musters et al. [17] searched the effect of rLH on embryo quality in women with POR. However, this study found no significant difference in embryo quality after adding rLH to rFSH for ovarian stimulation in women with POR. In addition, a study demonstrates that adding rLH to rFSH in GnRH antagonist protocols significantly improves cumulative live birth rates in IVF cycles. It found that rLH supplementation not only enhanced embryo quality but also increased live birth rates in both fresh and frozen-thawed embryo transfers without raising the risk of severe complications such as ovarian hyperstimulation syndrome or increasing cycle cancellation rates [18]. In contrast to this, one study directly compared embryonic quality in IVF cycles using rFSH or hMG in a GnRH antagonist protocol. The results showed that while the total embryo score was similar between the two groups, the best embryo score and the total number of embryos were significantly higher in the rFSH group. This suggests that rFSH may be more effective in enhancing certain aspects of embryo quality compared to hMG, though both led to similar pregnancy rates [19].

One of the limitations of our study was that it was a retrospective study. When we looked at the files of the patients, we saw that the embryos were transferred on the 3rd day cleavage stage in all patients. Comparing the embryos that could reach the 5th day of the blastocyst stage for both drug groups could have given us information about the preferability of hp-hMG and rFSH to each other. The strength of our study is that it is a single center, single doctor study.

Conclusion

In conclusion, our recommendation as a result of this study is that neither drug group is superior to each other in terms of pregnancy parameters in patients with POR. We can use both drug types for IVF cycles of poor ovarian reserve patients. However, more studies are needed to say that hp-hMG provides the same stimulation and pregnancy parameters as rFSH at a lower cost.

References

1. Keay SD, Liversedge NH, Mathur RS et al. Assisted conception following poor ovarian response to gonadotrophin stimulation. Br J Obstet Gynaecol 1997; 104(5): 521–527. doi: 10.1111/j.1471-0528.1997.tb11525.x.
2. Ferraretti AP, La Marca A, Fauser BC et al. ESHRE working group on Poor Ovarian Response Definition. 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. doi: 10.1093/humrep/der092.
3. De Placido G, Alviggi C, Mollo A et al. Recombinant follicle stimulating hormone is effective in poor responders to highly purified follicle stimulating hormone. Hum Reprod 2000; 15(1): 17–20. doi: 10.1093/humrep/15.1.17.
4. Bjercke S, Tanbo T, Åbyholm T et al. Clinical outcome following stimulation with highly purified hMG or recombinant FSH in patients undergoing their first treatment cycle of IVF or ICSI. Acta Obstet Gynecol Scand 2010; 89(8): 1053–1060. doi: 10.3109/00016349.2010.499450.
5. Hillier SG. Gonadotropic control of ovarian follicular growth and development. Mol Cell Endocrinol 2001; 179(1–2): 39–46. doi: 10.1016/s0303-7207(01)00469-5.
6. Conforti A, Esteves SC, Humaidan P et al. Recombinant human luteinizing hormone co-treatment in ovarian stimulation for assisted reproductive technology in women of advanced

reproductive age: a systematic review and meta-analysis of randomized controlled trials. Reprod Biol Endocrinol 2021; 19(1): 91. doi: 10.1186/s12958-021-00759-4.
7. Conforti A, Esteves SC, Di Rella F et al. The role of recombinant LH in women with hypo-response to controlled ovarian stimulation: a systematic review and meta-analysis. Reprod Biol Endocrinol 2019; 17(1): 18. doi: 10.1186/s12958-019-0460-4.
8. Ovarian TEGGO, Bosch E, Broer S et al. ESHRE guideline: ovarian stimulation for IVF/ICSI. Hum Reprod Open 2020; 2020(2): hoaa009. doi: 10.1093/hropen/hoaa009.
9. Ye H, Huang G, Pei L et al. Outcome of *in vitro* fertilization following stimulation with highly purified hMG or recombinant FSH in downregulated women of advanced reproductive age: a prospective, randomized and controlled trial. Gynecol Endocrinol 2012; 28(7): 540–544. doi: 10.3109/09513590.2011.650742.
10. Ji Z, Quan X, Lan Y et al. Gonadotropin versus follicle-stimulating hormone for ovarian response in patients undergoing *in vitro* fertilization: a retrospective cohort comparison. Curr Ther Res Clin Exp 2019; 92: 100572. doi: 10.1016/j.curtheres.2019.100572.
11. 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. doi: 10.1093/humrep/dev038.
12. Çelik C, Sofuoğlu K, Selçuk S et al. Comparison of ovulation induction and pregnacy outcomes in IVF patients with normal ovarian reserve who underwent long protocol with recombinant-FSH and highly purified-hMG. J Turk Ger Gynecol Asso 2011; 12(1): 15–20. doi: 10.5152/jtgga.2011.04.
13. Al-Inany HG, Abou-Setta AM, Aboulghar MA et al. Efficacy and safety of human menopausal gonadotrophins versus recombinant FSH: a meta-analysis. Reprod Biomed Online 2008; 16(1): 81–88. doi: 10.1016/s1472-6483(10)60559-7.
14. van Wely M, Kwan I, Burt AL et al. Recombinant versus urinary gonadotrophin for ovarian stimulation in assisted reproductive technology cycles. Cochrane Database Syst Rev 2011; 2011(2): CD005354. doi: 10.1002/14651858.CD005354.pub2.
15. Wu X, Chen Y, Zhou X et al. Timing of HMG supplementation and clinical outcomes of advanced-age patients with diminished ovarian reserve receiving gonadotropin-releasing hormone antagonist protocol. Nan Fang Yi Ke Da Xue Bao 2021; 41(3): 412–417. doi: 10.12122/j.issn.1673-4254.2021.03.14.
16. Kan O, Simsir C, Atabekoglu CS et al. The impact of adding hp-hMG in r-FSH started GnRH antagonist cycles on ART outcome. Gynecol Endocrinol 2019; 35(10): 869–872. doi: 10.1080/09513590.2019.1600667.
17. Musters AM, van Wely M, Mastenbroek S et al. The effect of recombinant LH on embryo quality: a randomized controlled trial in women with poor ovarian reserve. Hum Reprod 2012; 27(1): 244–250. doi: 10.1093/humrep/der371.
18. Wang M, Huang R, Liang X et al. Recombinant LH supplementation improves cumulative live birth rates in the GnRH antagonist protocol: a multicenter retrospective study using a propensity score-matching analysis. Reprod Biol Endocrinol 2022; 20(1): 114. doi: 10.1186/s12958-022-00985-4.
19. Chapon RD, Genro VK, de Souza CA et al. Randomized controlled trial comparing embryonic quality in rFSH versus hMG in the IVF protocol with GnRH antagonist. JBRA Assist Reprod 2021; 25(1): 131–135. doi: 10.5935/1518-0557.20200064.

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DGK, OG designed study.
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MST analysed data.
MST prepared figures and tables.
OG, HA supervised research.
DGK, MST, SD wrote manuscript.
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