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ORIGINAL RESEARCH

Assisted Reproductive Technology Outcomes in Women with Normal Ovarian Response Receiving Recombinant Luteinizing Hormone/Human Menopausal Gonadotropin: An Observational Study

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Objective: Additive human menopausal gonadotropin (HMG)/recombinant luteinizing hormone (r-LH) to follicle-stimulating hormone (FSH) can improve pregnancy outcomes in patients with poor ovarian response during assisted reproductive procedures. However, their effects on patients with normal ovarian response during such procedures are unclear, which formed the aim of this study.

Methods: This retrospective study enrolled 456 infertile women who underwent in vitro fertilization or intracytoplasmic sperm injection treatment. Group 1 received FSH; Group 2 received FSH+HMG/r-LH; Group 3 received FSH+HMG+r-LH.

Results: The age and Body Mass Index were significantly greater in Group III. The endometrial thickness was greater in Groups II and III, suggesting better endometrial receptivity. Better pregnancy and birth outcomes were seen in Group 3. In sub-cohorts of women older than 32 years old or with overweight/obesity, pregnancy and birth outcomes were also much better in Group 3, albeit without statistical significance.

Conclusion: The addition of both HMG and r-LH to FSH may improve the chance of infertile women with normal ovarian responses to have more success in having live birth babies, specifically in those over 32 years of age or with overweight/obese patients who typically face challenges in conceiving and sustaining a pregnancy.

Keywords: in vitro fertilization, intracytoplasmic sperm injection, live birth rate, cumulative live birth rate

Introduction

Infertility affects approximately 15% of couples worldwide,[1] who can achieve pregnancy via assisted reproduction techniques. In patients with a normal ovarian response, the prolonged gonadotropin-releasing hormone agonist (GnRH-a) protocol is the most commonly used protocol for in vitro fertilization-embryo transfer (IVF-ET) procedure.[2,3] However, GnRH-a may lead to over-suppression of luteinizing hormone (LH), negatively impacting IVF-ET outcome.[4] Optimal LH activity is critical for the quality and function of oocytes,[5] and cell proliferation and cytoplasmic maturation of oocytes.[6]

During ovarian stimulation, LH administration varies in dose and timing.[7] Nevertheless, adding LH to follicle-stimulating hormone (FSH) can improve ovarian function in patients with a poor ovarian response,[8] by increasing the mature egg rate, embryo quality,[9] and implantation rate.[10] Additive recombinant (r)-LH during controlled ovarian stimulation can obtain >5 oocytes.[11] In women aged >35 years, LH supplementation can improve clinical pregnancy and ongoing pregnancy rates.[8]

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Before r-LH was available, human menopausal gonadotropin (HMG) was once the only option for stimulating LH activity,[12] which significantly improved clinical pregnancy rates than FSH alone in women with normal gonadotropic responses.[13] When using the GnRH-antagonist protocol, r-LH seemed to result in a higher cumulative live birth rate than HMG.[14] However, when using the early-follicular phase prolonged GnRH-a protocol, the optimal choice between r-LH, HMG, or combined is unclear for women with normal ovarian response.

Herein, we explored the pregnancy outcomes and medical costs in women with normal ovarian response who received various early-follicular phase prolonged GnRH-a protocols.

Materials and Methods

Study Design and Population

In the retrospective observational study, women who received IVF or ICSI treatments with early-follicular phase prolonged GnRH-a protocols were included from the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University between February 1, 2021 and March 31, 2022. This research was conducted in accordance with the Declaration of Helsinki, and approved by the Medical Ethics Committee of the Second Affiliated Hospital of Wenzhou Medical University (2022-K-53-01). Informed consent was obtained from all women.

The inclusion criteria were as follows: (1) 18–40 years old; (2) infertility due to tubal dysfunction or unexplained factor in women with normal ovarian response; (3) the FSH ≤10 U/L, FSH/LH ratio ≤3, anti-Müllerian hormone (AMH) ≥1.5 ng/mL, and antral follicular count (AFC) ≥7 on cycle days 2–5. The exclusion criteria were: (1) women with obesity [body mass index (BMI) ≥30 kg/m^2] (greater difficulties in IVF success in all populations[15,16]); (2) only one ovary; (3) polycystic ovary syndrome; (4) grade 3–4 endometriosis; or (5) metabolic or autoimmune diseases. According to the treatments, women were divided into the FSH (Group I), FSH+HMG/r-LH (Group II), and FSH+HMG+r-LH (Group III).

Treatment Protocols

GnRH-a (3.75mg once, Triptorelin, Germany) was administered on days 2–5 of the menstrual cycle.[17] After 30–37 days, pituitary downregulation was achieved, reflected by antral follicles ≤5mm, serum estradiol <50pg/mL, serum LH=5U/L, and the endometrial thickness <5mm. Then, gonadotropin treatment started, using the FSH (Gonal-F; Merck Serono, Switzerland), HMG (hMG; Lizhu Pharma, China), and r-LH (Merck Serono). The preliminary dose was based on age, antral follicular count, and BMI. Follicle development was monitored. Gonadotropin dose was titrated according to follicle growth by transvaginal ultrasound and serum levels of estradiol, LH, FSH, and progesterone. When one dominant follicle reached 18 mm in diameter or two leading follicles reached ≥17mm in diameter, HMG (4000–10,000U) was administered to trigger final oocyte maturation, and oocytes were retrieved 36–38h later. One day later, luteal phase support started using dydrogesterone (40mg twice daily, Solvay, Netherlands) and progesterone (200mg daily, Cyndea Pharma, Spain).

At 4–6h after retrieval, the oocytes were fertilized by IVF or ICSI. Embryos were cultured at 37°C under standard condition and scored by the Alpha Scientists in Reproductive Medicine and ESHRE Special Interest Group of Embryology.[18] Following fertilization, two prokaryotes and two polar bodies were detected 16–18h later as a sign of normal fertilization. Embryo were scored by the number, size, and shape of blastomeres and the proportion of fragments at the cleavage stage.[18,19] The high-quality embryo was characterized by four blastomeres on day 2, ≥7 blastomeres on day 3 with a normal zona pellucida, <20% of fragments, and a complete absence of multinucleated blastomeres at any stage of early cleavage.[18,20] The blastocyst was evaluated by the Gardner scoring system, including the degree of blastocoel expansion, the size and density of inner cell masses, and the density and number of cells in the trophoblastic layer.[18,21] The blastocyst was transferred 5 days after incubation.

The frozen-thawed embryo transfer was performed in women who failed fresh embryo transfer. Hormone replacement therapy was used to prepare the endometrium, starting with estradiol valerate from day 2–5 of the cycle (4 mg/day oral, Femoston; Abbott Biological, China) to day 14 after embryo transfer, titrated by endometrial thickness every 3–5 days. After 12 days of treatment, when the endometrial thickness ≥8 mm and the progesterone <1.5 ng/mL a transformation of the endometrium started with dydrogesterone (20 mg/day oral, Abbott Biological) and progestin (400 mg oral/vaginal,

daily, Cyndea Pharma, Spain) or progesterone (90 mg sustained-release vaginal gel, daily, Fleet Laboratories, UK) daily for 3–5 days before embryo transfer.

Pregnancy was confirmed when serum human chorionic gonadotropin (hCG) level 14 days after blastocyst transfer and a gestational sac and cardiac pulsation via ultrasound at 4–5 weeks following transfer.

Data Collection

Data of women receiving IVF or ICSI treatments were collected in this current study. Before the treatments, the age (years), BMI (kg/m^2), infertility type (primary or secondary), baseline FSH (U/L), baseline LH (U/L), baseline FSH/LH ratio, baseline prolactin (ng/mL), baseline progesterone (ng/mL), baseline estradiol (pg/mL), baseline testosterone (ng/mL), AMH (ng/mL), and AFC were recorded. The LH (U/L), estradiol (pg/mL), progesterone (ng/mL), and number of follicles on the first day of GnRH-a were noted. During the ovarian stimulation, several parameters were recorded, including the preliminary GnRH-a dose (IU), maximum daily GnRH-a dose (IU), GnRH-a duration (days), total GnRH-a dose (IU), number of mature follicles ≥14 mm, estradiol (pg/mL), LH (U/L), progesterone (ng/mL), endometrial thickness (mm), retrieved oocytes, mature oocytes, fertilized oocytes, fertilization rate, number of total embryos, number of total high-quality embryos, high-quality embryo rate, blastocysts, blastocyst formation rate, and fresh embryo transfer cycles. The cost per embryo and blastocyst were also included. The pregnancy outcomes involved the rates of biochemical pregnancy, clinical pregnancy, live birth, and cumulative live birth. Biochemical pregnancy refers to pregnancy duration less than 12 weeks. The live birth rate was calculated as live births/fresh embryo transfer cycles. The cumulative live birth rate was the live births following the use of all fresh and frozen embryos derived from a single controlled ovarian stimulation cycle.[22]

Cost Calculation

Cost is one of major issues for IVF treatment.[23] In China, it is an out-of-pocket expense, costing 17,000–20,000 Chinese yuan (USD 2459–28,931). In contrast, the per capita disposable income was 35,128 yuan with the expenditure 24,100 yuan in 2021.[24] Therefore, IVF/intracytoplasmic sperm injection (ICSI)-ET treatment can impose significant financial stress on the average family, especially those with a single income, adversely affecting pregnancy outcomes resulting in repeated treatments. Repeated ovarian hyperstimulation can markedly affect the patient's health.[25] Therefore, patients prefer obtaining a decent number of embryos from one oocyte retrieval cycle. The direct medical costs were calculated based on the 2021 price in the two hospitals. The costs per oocyte retrieval cycle, per available embryo, and per blastocysts were reported.

Statistical Analysis

Continuous numerical variables are presented as mean±standard deviation and analyzed using one-way ANOVA with Tukey post hoc tests. Categorical variables are shown as the number (percentage) and analyzed using the Chi-square test (SPSS V24.0, IBM Corp., NY, USA). As increased age and BMI can increase the difficulties of conceiving, we also studied two sub-cohorts, those ≥32 years (when oocyte number decline accelerates)[26] and those with overweight (23 kg/m^2 ≤ BMI <30 kg/m^2). P<0.05 were considered statistically significant.

Results

Characteristics of Women with Normal Ovarian Response Who Received the IVF-ET

Of the total 456 women with normal ovarian response, 115 treated by FSH, 244 received the FSH+HMG/r-LH treatment, and 97 received FSH+HMG+r-LH treatment. Table 1 shows the characteristics of women with normal ovarian response who received the IVF-ET. The age, BMI, progesterone, preliminary GnRH-a dose, maximum daily GnRH-a dose, duration of GnRH-a, endometrial thickness, and blastocyst formation rate were statistical differences among the three groups (P <0.05). No differences were found in the rates of biochemical pregnancy, clinical pregnancy, live birth, and cumulative live birth among the three groups (P >0.05).

Table 1 Characteristics of Women with Normal Ovarian Response Who Received the IVF-ET

Variables	Group I (n=115)	Group II (n=244)	Group III (n=97)	*P*
Age (years), mean±SD	30.90±3.75	31.43±3.86	32.38±4.24[ab]*	0.023
BMI (kg/m^2), mean±SD	22.04±3.11	21.78±3.14	23.61±3.34[ab]**	<0.001
Type of infertility, n (%)				
Primary	46 (40.0)	113 (49.1)	19 (38.8)	
Secondary	69 (60.0)	117 (50.9)	30 (61.2)	
Baseline FSH (U/L), mean±SD	6.58±1.56	6.82±1.53	6.69±1.53	0.386
Baseline LH (U/L), mean±SD	4.51±2.18	4.75±2.41	4.98±2.46	0.362
Baseline FSH/LH ratio, mean±SD	1.67±0.60	1.66±0.60	1.58±0.62	0.512
Baseline prolactin (ng/mL), mean±SD	13.94±8.34	13.77±9.03	12.20±7.20	0.282
Baseline progesterone (ng/mL), mean±SD	0.54±0.33	0.69±1.52	0.95±2.10	0.214
Baseline estradiol (pg/mL), mean±SD	52.96±56.03	52.02±38.14	45.75±16.87	0.383
Baseline testosterone (ng/mL)	0.27±0.15	0.30±0.18	0.63±3.29	0.170
AMH (ng/mL), mean±SD	4.11±2.42	4.04±2.52	3.96±2.63	0.921
AFC (n), mean±SD	15.72±4.55	14.99±5.30	15.25±4.94	0.667
GnRH-a on day 1				
LH (U/L), mean±SD	0.78±0.79	0.91±5.23	0.32±0.35	0.499
Estradiol (pg/mL), mean±SD	27.80±17.93	32.52±89.46	23.47±9.27	0.555
Progesterone (ng/mL), mean±SD	0.41±0.18	0.54±0.47[a]*	0.46±0.28	0.025
Follicles (n), mean±SD	16.00±4.47	16.00±5.53	16.62±5.49	0.610
During ovarian stimulation				
Preliminary GnRH-a dose (IU), mean±SD	168.48±43.44	192.98±52.75[a]**	200.64±67.37[a]**	<0.001
Maximum daily GnRH-a dose (IU), mean±SD	188.26±45.17	248.21±59.93[a]**	278.87±65.16[ab]**	<0.001
Duration of GnRH-a (days), mean±SD	10.12±2.00	11.43±2.55[a]**	12.53±2.14[ab]**	<0.001
Total GnRH-a dose (IU), mean±SD	1789±569	2447±1068[a]**	2834±978[ab]**	<0.001
Mature follicles ≥ 14 mm (n), mean±SD	10.88±3.91	11.07±4.44	10.38±4.23	0.431
Estradiol (pg/mL), mean±SD	2821±1256	2764±1314	2568±1426	0.389
LH (U/L), mean±SD	1.69±2.43	1.91±12.62	0.63±0.43	0.554
Progesterone (ng/mL), mean±SD	0.86±0.40	6.01±72.91	0.65±0.42	0.629
Endometrial thickness (mm), mean±SD	10.31±2.81	11.30±2.48[a]*	11.14±2.67[a]*	0.002
Retrieved oocytes, mean±SD	15.10±6.19	14.61±5.43	14.55±4.67	0.700
Mature oocytes, mean±SD	12.90±5.43	12.72±4.95	12.67±5.66	0.941
Fertilized oocytes, mean±SD	10.57±4.61	10.47±4.41	10.45±4.99	0.975
Fertilization rate (%), mean±SD	83.01±13.07	82.53±13.47	82.17±11.68	0.919
Total embryos, mean±SD	10.35±4.61	10.23±4.27	10.16±4.91	0.955
Total high-quality embryos, mean±SD	8.39±4.16	7.86±3.82	7.91±3.91	0.222
High-quality embryo rate (%), mean±SD	81.21±17.80	76.70±19.26	78.23±21.00	0.116
Blastocysts, mean±SD	5.55±2.98	4.84±2.85	4.73±3.24	0.069
Blastocyst formation rate (%)	54.22±21.02	48.13±22.26[a]*	49.77±21.42	0.049
Fresh embryo transfer cycles, n	83	197	66	
Pregnancy outcomes				
Biochemical pregnancy, n (%)	68/83 (81.9)	149/197 (75.6)	53/66 (80.3)	0.426
Clinical pregnancy, n (%)	55/83 (66.3)	123/197 (62.4)	46/66 (69.7)	0.749
Live birth, n (%)	46/83 (55.4)	110/197 (55.8)	40/66 (60.6)	0.819
Cumulative live birth, n (%)	78/115 (67.8)	161/244 (66.0)	56/90 (62.2)	0.978

Notes: *P<0.05, **P<0.001. [a]vs. Group I. [b]vs. Group II. Group I: FSH; group II: FSH+HMG/r-LH; group II: FSH+HMG+r-LH.
Abbreviations: SD, standard deviation; BMI, body mass index; FSH, follicle-stimulating hormone; HMG, human menopausal gonadotropin; r-LH, recombinant luteinizing hormone; AMH, anti-Mullerian hormone; AFC, antral follicle count; LH, luteinizing hormone.

Characteristics of Women Aged ≥32 Years or Overweight

The characteristics of women aged ≥32 years or overweight were shown in Table 2. The average age in Group III was 35, versus 34 in Groups 1 and 2 (P<0.05 vs Groups I). BMI was also much bigger in the Group III (P<0.05, vs both groups). Endometrial thickness was still greater in the Groups II and III (both P<0.05 vs Group I). Blastocyst formation rate and

Table 2 Characteristics of Women Aged ≥32 Years and Overweight

Variables	Age ≥32 Years				Overweight			
	Group I (n=115)	Group II (n=244)	Group III (n=97)	*P*	Group I (n=115)	Group II (n=244)	Group III (n=97)	*P*
Age (years), mean±SD	34.25±1.93	34.61±2.12	35.28±2.57[a]*	0.045	31.34±3.32	31.85±4.06	31.67±4.41	0.803
BMI (kg/m^2), mean±SD	22.09±2.94	21.76±3.12	23.39±3.40[ab]*	0.006	25.67±2.15	25.43±2.03	25.93±1.85	0.293
Endometrial thickness (mm), mean±SD	9.70±2.93	11.10±2.55[a]*	11.05±2.16[a]*	0.009	10.82±3.29	11.36±2.39	11.79±3.00	0.190
Blastocysts, mean±SD	5.55±2.83	4.73±2.81	4.91±3.24	0.245	5.32±2.78	5.09±2.70	4.55±3.14	0.772
Blastocyst formation rate (%), mean±SD	55.68±20.62	47.99±22.81	45.17±20.61	0.058	55.39±21.18	52.25±23.96	50.16±24.70	0.659
Fresh embryo transfer cycles (n)	37	101	39		28	60	36	
Biochemical pregnancy, n (%)	29/37 (78.4)	74/101 (73.3)	30/39 (76.9)	0.793	20/28 (71.4)	46/60 (76.7)	30/36 (83.3)	0.518
Clinical pregnancy, n (%)	22/37 (59.5)	61/101 (60.4)	26/39 (66.7)	0.757	15/28 (53.6)	31/60 (51.7)	26/36 (72.2)	0.122
Live birth, n (%)	17/37 (45.9)	53/101 (52.5)	21/39 (53.8)	0.748	11/28 (39.3)	28/60 (46.7)	24/36 (66.7)	0.063
Cumulative live birth, n (%)	29/51 (56.9)	72/123 (58.5)	31/54 (57.4)	0.976	24/38 (63.2)	54/79 (68.4)	34/51 (66.7)	0.976

Notes: *P<0.05, **P<0.001. [a]vs. Group I. [b]vs. Group II. Group I: FSH; group II: FSH+HMG/r-LH; group II: FSH+HMG+r-LH.
Abbreviations: SD, standard deviation; BMI, body mass index.

biochemical pregnancy rate were highest in Group I; however, the clinical pregnancy rate was highest in Group III. Live birth rate and cumulative live birth rate were higher in Groups II and III, albeit without statistical significance.

There was no difference in the age or BMI among the 3 groups. The endometrial thickness appears greater in Groups II and III. The number of blastocysts and blastocyst formation rate were similar among the three groups. Group III showed the highest biochemical pregnancy rate, clinical pregnancy rate, and live birth rate (P=0.063); however, the cumulative live birth rate was similar between the three groups.

Direct Medical Costs for Oocyte Retrieval

Table 3 shows the direct medical costs for oocyte retrieval. There were statistical differences of the direct medical costs among the three groups in per oocyte retrieval cycle, per embryo and per blastocyst (P<0.05). Compared with the Groups II, the costs of per oocyte retrieval cycle (17,052 vs 14,940), per embryo (2264 vs 1826) and per blastocyst (5304 vs 3874) were higher in the Group III.

Discussion

In this current study, the endometrial thickness in women with normal ovarian response who receiving the FSH+HMG/r-LH or FSH+HMG+r-LH was thicker in comparison to those who receiving the FSH. Women with the two therapies had higher pregnancy and live birth rates, specifically among patients older than 32 years or overweight who normally face challenges in conceiving and sustaining a pregnancy. Here, the participants were unique, who had normal ovarian responses, by Bologna criteria[27] and POSEIDON classification.[28] The strength lies in the same controlled ovarian stimulation protocol used for all patients undergoing IVF/ICSI, ie early follicular phase prolonged GnRH-a protocol, allowing valid comparisons between the groups.

The major benefit of adding both HMG and r-LH to FSH is the improvement in endometrial thickness. Endometrial receptivity is a major factor affecting IVF/ICSI success.[29] Poor endometrial receptivity and abnormal embryo-

Table 3 Direct Medical Costs for Oocyte Retrieval

Variables	Group I (n=115)	Group II (n=244)	Group III (n=97)	*P*
Oocyte retrieval cycle (CNY/per), mean±SD	14940±1983	15,524±1996[a]*	17,052±2325[ab]**	<0.001
Embryo (CNY/per), mean±SD	1826±1099	1860±1018	2264±1654[ab]*	0.011
Blastocyst (CNY/per), mean±SD	3874±3314	4610±3685	5304±4467 [a]*	0.026

*P<0.05, **P<0.001. [a]vs. Group I. [b]vs. Group II. Group I: FSH; group II: FSH+HMG/r-LH; group II: FSH+HMG+r-LH.
Abbreviation: SD, standard deviation.

endometrial interaction account for two-thirds of implantation failures.[29] LH can increase the de novo ovarian progesterone synthesis to regulate ovarian growth and differentiation after ovulation, which is critical in endometrium preparation for implantation and maintenance of pregnancy.[30] Low LH levels can inhibit endometrial growth and even stagnation, impairing endometrium receptivity[31] and implantation rate.[32] Our findings are consistent with a meta-analysis[33] where in patients >30 years old, the FSH+HMG+r-LH improved endometrial thickness. Ata et al[34] reported no linear relationship of endometrial thickness with live birth rate, and no predictive value of endometrial thickness for live birth rate. Gursu et al[35] mentioned that the endometrial thickness measurement in patients undergoing the infertility treatment may provide little benefit to clinical outcomes. Previous studies showed that endometrial thickness on the day of hCG administration can be a potential prognostic tool for the outcomes of the assisted reproductive technology, which serve as an indicator of endometrial receptivity.[36,37] Further studies need to validate our findings.

Sufficient LH is also required to support follicle development and oocyte maturation,[6,38–40] and facilitate the meiosis and extrusion of the first polar body.[41] The blastocyst formation rate is closely related to pregnancy outcomes.[42] Live birth is the ultimate goal for IVF/ICSI treatment.[43] Our results show that clinical pregnancy and live birth rates were highest in the FSH+HMG+r-LH group, albeit marginal impact on blastocyst formation. However, HMG and/or r-LH showed a marginal benefit in the cumulative live birth rate for those having multiple transfers, maybe related to the small sample size. It is still reasonable to postulate that HMG+r-LH promote optimal embryo and pregnancy success.

The dosage and duration of gonadotropin needed can reflect ovarian response. Groups II and III required more gonadotropin, suggesting some impaired ovarian response albeit clinicaly classified as “normal”. Thus, additional hormone(s) (HMG and/or r-LH) is necessary to achieve optimal pregnancy outcomes. Age and BMI may play a role, both of which affect fertility and IVF/ICSI success.[44–46] Overweight/obese patients benefit from additional r-LH to improve embryo quality and ongoing pregnancy rates.[47] Here, adding HMG and/or r-LH appeared to improve the clinical pregnancy rate and live birth rate in the sub-cohort of obese/overweight women. The lack of statistical significance is primarily due to the small sample size. However, for clinicians, the physiological significance is more important than the statistical significance regarding the patient’s outcome. Age also affects IVF-ET success,[48] as oocyte quantity and number decline with age.[49] At 32 years, there is a marked decline in oocyte number.[26] Indeed, the sub-cohort (32–40 years old) had lower pregnancy and live birth rates compared with the whole cohort. Group III were also older and heavier than those in Groups I and II, yet without differences in the live birth rate or cumulative live birth rate. Thus, it was reasonable to postulate that in “normal” ovarian responders, adding HMG and rLH can compensate for the age effects on pregnancy outcomes, helping older women achieve comparable live birth and cumulative live birth rate to young women.

Assisted reproductive treatment is costly. The extra embryos will be frozen between transfers or when ovarian hyperstimulation syndrome or excessive trigger day progesterone elevation occurs. For a second transfer, additional costs included embryo freezing (~1500–2000/freezing) and transfer (~6000/procedure), far cheaper than another IVF-ET (min 14,000 yuan). Therefore, an optimal protocol to maximize the live birth rate is more cost-saving than repeated IVF/ICSI procedures.

We acknowledge that our group size was relatively small, especially when sub-cohorts were studied. Secondly, the study was retrospective when the treatment decision was made rather than a by randomization design, which can be addressed by future prospective studies to verify our results.

Conclusion

Adding HMG and/or r-LH to FSH can promote endometrial receptivity and pregnancy outcomes in women with normal ovarian responders, specifically those overweight and ≥32 years. Such practice may be cost-saving for couples aiming for multiple babies.

Abbreviations

FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; GnRH-a, GnRH agonist; hCG, human chorionic gonadotropin; HMG, menopausal gonadotropin; ICSI, intracytoplasmic sperm injection; LH, luteinizing hormone; IVF-ET, in vitro fertilization-embryo transfer; r-LH, recombinant luteinizing hormone.

Data Sharing Statement

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

Ethics Approval and Consent to Participate

This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethic committee of the Second Affiliated Hospital of Wenzhou Medical University (2022-K-53-01). The written informed consent was obtained from the participants.

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Disclosure

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References

1. Harris E. Infertility affects 1 in 6 people globally. *JAMA*. 2023;329(17):1443.
2. La marca A, Sunkara SK. Individualization of controlled ovarian stimulation in IVF using ovarian reserve markers: from theory to practice. *Human Reproduction Update*. 2014;20(1):124–140. doi:10.1093/humupd/dmt037
3. Massin N. New stimulation regimens: endogenous and exogenous progesterone use to block the LH surge during ovarian stimulation for IVF. *Hum Reprod Update*. 2017;23(2):211–220. doi:10.1093/humupd/dmw047
4. Nargund G, Datta AK, Fauser B. Mild stimulation for in vitro fertilization. *Fertil Steril*. 2017;108(4):558–567. doi:10.1016/j.fertnstert.2017.08.022
5. Bosch E, Labarta E, Crespo J, Simón C, Remohí J, Pellicer A. Impact of luteinizing hormone administration on gonadotropin-releasing hormone antagonist cycles: an age-adjusted analysis. *Fertil Sterility*. 2011;95(3):1031–1036. doi:10.1016/j.fertnstert.2010.10.021
6. Huang Y, Zhao Y, Yu Y, et al. Altered amphiregulin expression induced by diverse luteinizing hormone receptor reactivity in granulosa cells affects IVF outcomes. *Reprod Biomed Online*. 2015;30(6):593–601. doi:10.1016/j.rbmo.2015.03.001
7. Behre HM, Howles CM, Longobardi S. Randomized trial comparing luteinizing hormone supplementation timing strategies in older women undergoing ovarian stimulation. *Reprod Biomed Online*. 2015;31(3):339–346. doi:10.1016/j.rbmo.2015.06.002
8. Lehert P, Kolibianakis EM, Venetis CA, 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;12(1):17. doi:10.1186/1477-7827-12-17
9. Canosa SCA, Mercaldo N, Mercaldo N, et al. Effect of rLH supplementation during controlled ovarian stimulation for IVF: evidence from a retrospective analysis of 1470 poor/suboptimal/normal responders receiving either rFSH plus rLH or rFSH Alone. *J Clin Med*. 2022;11(6):1575. doi:10.3390/jcm11061575
10. Bühler K, 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. *Gynecological Endocrinol*. 2012;28(5):345–350. doi:10.3109/09513590.2011.633128
11. Mennini FS, Marcellusi A, Viti R, et al. Probabilistic cost-effectiveness analysis of controlled ovarian stimulation with recombinant FSH plus recombinant LH vs. human menopausal gonadotropin for women undergoing IVF. *Reprod Biol Endocrinol*. 2018;16(1):68. doi:10.1186/s12958-018-0386-2
12. Tayyar KS, 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. doi:10.5114/aoms.2017.72408
13. Polyzos NP, De Vos M, Corona R, 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. doi:10.1093/humrep/det045
14. Chen MJ, Yi YC, Guu HF, et al. A retrospective, matched case-control study of recombinant LH versus hMG supplementation on FSH during controlled ovarian hyperstimulation in the GnRH-antagonist protocol. *Front Endocrinol*. 2022;13:931756. doi:10.3389/fendo.2022.931756
15. Pandey S, Pandey S, Maheshwari A, Bhattacharya S. The impact of female obesity on the outcome of fertility treatment. *J Hum Reprod Sci*. 2010;3(2):62–67. doi:10.4103/0974-1208.69332
16. Hu D, Huang B, Xiong M, et al. Impact of elevated body mass index on cumulative live birth rate and obstetric safety in women undergoing assisted reproductive technology. *Sci Rep*. 2022;12(1):18858. doi:10.1038/s41598-022-23576-0
17. Ma H, Mao R, Wang R, et al. Effects of inactivated COVID-19 vaccinations on the IVF/ICSI-ET live birth rate and pregnancy complication in a population of southern China: a retrospective cohort study. *J Evid Based Med*. 2023;16(2):107–110. doi:10.1111/jebm.12528
18. Balaban B, Brison D, Calderon G. Medicine ASiR, Embryology ESIGo: the Istanbul consensus workshop on embryo assessment: proceedings of an expert meeting†. *Hum Reprod*. 2011;26(6):1270–1283. doi:10.1093/humrep/der037
19. Davis OK, Brinsden PR. A textbook of in vitro fertilization and assisted reproduction. new york: the Parthenon publishing group, 1999:1–564. Price: $110.00. *Fertil Sterility*. 2000;73(6):1270–1271. doi:10.1016/S0015-0282(00)00474-X

20. De Neubourg DGJ, Mangelschots K, Van Royen E, Vercruyssen M, Elseviers M. Single top quality embryo transfer as a model for prediction of early pregnancy outcome. *Hum Reprod*. 2004;19(6):1476–1479. doi:10.1093/humrep/deh283
21. Gardner DLM, Stevens J, Stevens J, et al. Blastocyst score affects implantation and pregnancy outcome: towards a single blastocyst transfer[J]. *Fertil Steril*. 2000;73(6):1155–1158. doi:10.1016/S0015-0282(00)00518-5
22. Yang C, Dong N, Li F, Ji Y, Pan Y, She H. The cumulative live birth rate of recombinant follicle-stimulating hormone alfa verse urinary human follicle-stimulating hormone for ovarian stimulation in assisted reproductive technology cycles. *J ovarian Res*. 2022;15(1):74. doi:10.1186/s13048-022-01009-w
23. Aalabaf-Sabaghi M. Decision modelling for health economic evaluation. *Br J Soc Med*. 2007;61:9.
24. National bureau of statistics of china: households' income and consumption expenditure in 2021; 2022. Available from: http://wwwstatsgovcn/english/PressRelease/202201/t20220118_1826649html. Accessed June 4, 2024.
25. Gameiro S, Finnigan A. Long-term adjustment to unmet parenthood goals following ART: a systematic review and meta-analysis. *Human Reproduction Update*. 2017;23(3):322–337. doi:10.1093/humupd/dmx001
26. Owen A, Sparzak PB. Age-Related Fertility Decline. In: *Paul Sparzak Declares No Relevant Financial Relationships with Ineligible Companies*. Treasure Island (FL): StatPearls Publishing; Copyright © 2023, StatPearls Publishing LLC; 2023.
27. Ferraretti AP, La Marca A, Fauser BC, Tarlatzis B, Nargund G, Gianaroli 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. doi:10.1093/humrep/der092
28. Esteves SC, Alviggi C, Humaidan P, et al. The POSEIDON criteria and its measure of success through the eyes of clinicians and embryologists. *Front Endocrinol*. 2019;10:814. doi:10.3389/fendo.2019.00814
29. Craciunas L, Gallos I, Chu J, Bourne T, Quenby S, Brosens JJ. Coomarasamy A: conventional and modern markers of endometrial receptivity: a systematic review and meta-analysis. *Human Reproduction Update*. 2019;25(2):202–223. doi:10.1093/humupd/dmy044
30. Kundu S, Pramanick K, Paul S, Bandyopadhyay A, Mukherjee D. Expression of LH receptor in nonpregnant mouse endometrium: LH induction of 3β-HSD and de novo synthesis of progesterone. *J Endocrinol*. 2012;215(1):151–165. doi:10.1530/JOE-11-0486
31. Freis A, Germeyer A, Jauckus J, et al. Endometrial expression of receptivity markers subject to ovulation induction agents. *Arch Gynecol Obstetrics*. 2019;300(6):1741–1750. doi:10.1007/s00404-019-05346-y
32. Tesarik J, Hazout A, Mendoza C. Luteinizing hormone affects uterine receptivity independently of ovarian function. *Reprod Biomed Online*. 2003;7(1):59–64. doi:10.1016/S1472-6483(10)61729-4
33. Wang Y, Li L, Deng K, et al. Comparison of the combination of recombinant follicle-stimulating hormone and recombinant luteinizing hormone protocol versus human menopausal gonadotropin protocol in controlled ovarian stimulation: a systematic review and meta-analysis. *J Evid Based Med*. 2020;13(3):215–226. doi:10.1111/jebm.12390
34. Ata B, Liñán A, Kalafat E, et al. Effect of the endometrial thickness on the live birth rate: insights from 959 single euploid frozen embryo transfers without a cutoff for thickness. *Fertil Steril*. 2023;120(1):91–98. doi:10.1016/j.fertnstert.2023.02.035
35. Gursu T, Goksever Celik H, Eraslan A, et al. Impact of endometrial thickness change in response to progesterone on live birth rates embryo transfers with fresh oocyte donation cycles. *J Obstet Gynaecol*. 2022;42(7):3260–3267. doi:10.1080/01443615.2022.2112022
36. Ribeiro VC, Santos-Ribeiro S, De Munck N, et al. Should we continue to measure endometrial thickness in modern-day medicine? The effect on live birth rates and birth weight. *Reprod Biomed Online*. 2018;36(4):416–426. doi:10.1016/j.rbmo.2017.12.016
37. Simeonov M, Sapir O, Lande Y, et al. The entire range of trigger-day endometrial thickness in fresh IVF cycles is independently correlated with live birth rate. *Reprod Biomed Online*. 2020;41(2):239–247. doi:10.1016/j.rbmo.2020.04.008
38. Messinis IE, Messini CI, Dafopoulos K. The role of gonadotropins in the follicular phase. *Ann. N.Y. Acad. Sci.* 2010;1205(1):5–11. doi:10.1111/j.1749-6632.2010.05660.x
39. Loumaye E, Engrand P, Shoham Z, Hillier SG. Baird DT: clinical evidence for an LH 'ceiling' effect induced by administration of recombinant human LH during the late follicular phase of stimulated cycles in World Health Organization type I and type II anovulation. *Hum Reprod*. 2003;18(2):314–322. doi:10.1093/humrep/deg066
40. Palermo R. Differential actions of FSH and LH during folliculogenesis. *Reprod Biomed Online*. 2007;15(3):326–337. doi:10.1016/S1472-6483(10)60347-1
41. Filicori M. The role of luteinizing hormone in folliculogenesis and ovulation induction. *Fertil Steril*. 1999;71(3):405–414. doi:10.1016/S0015-0282(98)00482-8
42. Zhao J, Zhang Q, Wang Y, Li Y. Endometrial pattern, thickness and growth in predicting pregnancy outcome following 3319 IVF cycle. *Reprod Biomed Online*. 2014;29(3):291–298. doi:10.1016/j.rbmo.2014.05.011
43. Drakopoulos P, Errázuriz J, Santos-Ribeiro S, et al. Cumulative live birth rates in in-vitro fertilization. *Minerva ginecologica*. 2019;71(3):207–210. doi:10.23736/S0026-4784.18.04347-2
44. Meldrum DR. Introduction: obesity and reproduction. *Fertil Steril*. 2017;107(4):831–832. doi:10.1016/j.fertnstert.2017.02.110
45. Li Q, Guo S, Yang C, et al. High-fat diet-induced obesity primes fatty acid β-oxidation impairment and consequent ovarian dysfunction during early pregnancy. *Ann Translat Med*. 2021;9(10):887.
46. Broughton DE, Moley KH. Obesity and female infertility: potential mediators of obesity's impact. *Fertil Steril*. 2017;107(4):840–847. doi:10.1016/j.fertnstert.2017.01.017
47. Merve D, Emre S, Yucel COS, 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. *Open J Obst Gynecol*. 2020;10:4.
48. Vollenhoven B, Hunt S, Bollag L. Ovarian ageing and the impact on female fertility. *F1000Research*. 2018;7:7. doi:10.12688/f1000research.13350.2
49. Baird DT, Collins J, Egozcue J, Evers LH, Tarlatzis B. Fertility and ageing. *Human Reproduction Update*. 2005;11(3):261.