Impact of stimulation with luteinizing hormone activity on IVF outcomes in patients with polycystic ovary syndrome

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Abstract

Objective: To compare in-vitro fertilization (IVF) outcomes in polycystic ovary syndrome (PCOS) patients treated with follicle stimulating hormone (FSH) alone or FSH and luteinizing hormone (LH), under freeze-all gonadotropin-releasing hormone (GnRH) antagonist protocols.

Material and Methods: This retrospective study at a university center included PCOS patients, who underwent freeze-all GnRH antagonist IVF cycles between January 2013 and December 2019. They were divided into FSH-only and FSH + LH groups, focusing on pregnancy and live birth rates.

Results: The study included 82 patients: 43 received FSH + LH and 39 FSH only. Baseline characteristics were similar, except for higher thyroid stimulating hormone levels in the FSH-only group. The FSH + LH group required a lower mean ± standard deviation total dose of FSH (1271.5±376.7 vs. 1407.2±645.3 IU, p=0.02), had a shorter mean cycle length (7.3±3.4 vs. 8.3±1.6 days, p=0.004), and had a higher mean number of follicles stimulated (36.9±15.9 vs. 35.9±9.7, p=0.008) compared to the FSH-only group. No significant differences in pregnancy and live birth rates were noted at first transfer, but the cumulative live birth rate was significantly higher in the FSH-only group [30 of 39 (76.9%) vs. 24 of 43 (55.8%), p=0.044].

Conclusion: LH supplementation in PCOS patients undergoing GnRH antagonist IVF protocols may impair cumulative live birth rates, despite lowering FSH requirement and reducing IVF cycle length. These results highlight the complex role of LH in IVF outcomes for PCOS patients, suggesting a need for further large studies to fully understand the impact of LH in such treatments. (J Turk Ger Gynecol Assoc 2024; 25: 60-5)

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Introduction

Polycystic ovary syndrome (PCOS) is a prevalent condition in reproductive-age patients globally, with symptoms that vary, influencing its reported prevalence (1). Patients with PCOS exhibit increased luteinizing hormone (LH) pulsatility, characterized by more frequent pulses in all subjects and heightened amplitude, particularly in lean individuals (2). Elevated LH levels promote hyperandrogenism by stimulating theca cells, leading to increased intra-ovarian androgen levels (3). This hormonal imbalance, along with heightened serum LH, may contribute to disrupted granulosa cell function, increased oocyte atresia, and premature maturation of oocytes (4).

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In patients with PCOS undergoing in-vitro fertilization (IVF), concerns regarding oocyte quality and its impact on fertilization rates and outcomes have been noted (5). A previous study indicated that patients with PCOS experienced lower live birth rates per fresh embryo transfer compared to patients with normal ovulation and without PCOS (6).

The hypothesis that LH or LH activity in IVF stimulation could potentially lead to less favorable outcomes than follicle stimulating hormone (FSH) alone in patients with PCOS is based on the fact that PCOS is often associated with elevated LH levels, which can promote hyperandrogenism and potentially affect oocyte quality (3). Studies, including those by Singh et al. (7) and Sun et al. (8), have explored the role of high basal serum LH levels in PCOS on IVF outcomes, but these investigations found no significant differences in critical outcomes, such as clinical pregnancy and live birth rates. This suggests that the relationship between LH levels and IVF success in PCOS patients might be more complex than previously thought. However, it's important to note that basal LH levels can fluctuate in a pulsatile manner (9) and may not fully represent a patient's clinical status. To address this, the aim of our study was to specifically evaluate the impact of LH stimulation on IVF cycle outcomes in patients with PCOS.

Material and Methods

This was a retrospective cohort analysis at a single university center. It included patients treated between January 2013 and December 2019 who were diagnosed with PCOS based on the Rotterdam consensus criteria (10). The study focused on those who underwent freeze-all gonadotropin-releasing hormone (GnRH) antagonist IVF cycles, comparing outcomes between those who received FSH alone and those who received FSH combined with LH activity. In our study, LH activity was induced by administration of human chorionic gonadotropins (hCG) added to human menopausal gonadotropins (hMG) (Ferring Canada, Montreal, Canada), or as recombinant Lutropin-alpha (Merck Serono, Montreal, Canada).

The study was submitted and approved by the board of the McGill University Research Ethics Office (Internal Review Board) of the Faculty of Medicine and Health Sciences (approval number: 2020-5971).

In this study, PCOS was defined according to the 2003 Rotterdam criteria, which include any two of the following three features: oligo- or anovulation, signs of hyperandrogenism (either clinical or laboratory-based), and ultrasound evidence of polycystic ovaries, while ruling out other etiologies (10).

The study focused on patients undergoing freeze-all GnRH antagonist IVF cycles, specifically comparing the effects of FSH alone versus a combination of FSH and LH stimulation. This approach was chosen to isolate the impact of LH on the oocyte-follicle complex, eliminating potential LH effects on the endometrium. All eligible patients within the study period were included in the analysis.

For comprehensive data analysis, various factors were reviewed: patient age, gravida, parity, male partner's age, duration of infertility, basal levels of FSH, LH, estradiol, prolactin, thyroid stimulating hormone (TSH), total and free testosterone, and basal antral follicle count, along with sperm parameters, such as volume, concentration, and motility. This allowed for a detailed assessment of the influence of LH stimulation on IVF outcomes in the context of PCOS.

We excluded patients who did not meet the Rotterdam criteria for PCOS. In addition, we disregarded cases with incomplete cycle information (n=7), specifically those lacking details on secondary and primary outcomes. We also chose to exclude IVF cycles that resulted in fresh-embryo transfers. Furthermore, patients with untreated intra-cavity pathologies, such as fibroids or polyps, as well as males with severe male factor infertility (defined as less than 5 million total motile sperm count), were not included in the analysis.

Ovarian stimulation in our study was conducted using either recombinant follicle stimulating hormone (rFSH) (Follitropin Alpha by Merck Serono, Montreal, Canada, or Follitropin Beta by Organon, London, Canada), hMG (Menopur by Ferring, Montreal, Canada), or recombinant LH (Lutropin Alpha by Merck Serono, Montreal Canada). This began on day 3 of a fixed start antagonist protocol. The GnRH antagonist (either Cetrotide by Merck, Kirkland, Canada or Orgalutran by Organon, Kirkland, Canada) was introduced on cycle day 6. A normal baseline transvaginal ultrasound on day 2 or 3, confirming the absence of functional ovarian cysts, was a prerequisite for initiating IVF stimulation. The decision to add LH activity varied according to physician preference and was based on a combination of factors including patient age, ovarian reserve, previous response to stimulation, and specific clinical indications, aiming for a personalized treatment approach within the framework of the study.

Follicle monitoring via ultrasound commenced on cycle day 7 and was then adjusted based on ovarian response. 1000 IU subcutaneous injection of Buserelin (Sanofi-Aventis, North York, Canada) was used as a GnRH agonist for follicular maturation, and oocyte retrieval occurred 36 hours post-administration. Intracytoplasmic sperm injection (ICSI) was performed in cases of poor motility (<30%), and abnormal morphology, and after unsuccessful fertilization in previous IVF attempts without ICSI. All cycles in this study were freeze-all, with embryos being transferred in subsequent cycles.

The primary outcomes of the study were pregnancy and live birth rates. The pregnancy rate was determined by a positive serum hCG level of over 10 IU/L, measured 16 days after the

frozen embryo transfer. The clinical pregnancy rate is defined by ultrasound evidence of a gestational sac, embryo, and fetal heartbeat at 6 to 7 weeks of gestation. The live birth rate indicates a live child's birth after 24 weeks of gestation. Cumulative rates consider all outcomes from a single IVF cycle's embryos, with the clinical rate including early pregnancies confirmed by ultrasound and the live birth rate encompassing all live births from the cycle's embryos until they are fully utilized or result in a conception.

The study's secondary outcomes pertained to various elements of the IVF stimulation process, including the length of the IVF cycle, the total amount of gonadotropins administered, the highest estradiol level recorded during stimulation, and the maximal endometrial thickness observed on the day of ovulation induction. In addition, we assessed the total number of oocytes retrieved, the count of mature (MII) oocytes, the number of embryos that developed to the 2 pronuclei stage (2PN), and the total number of blastocysts that were cryopreserved. For cryopreservation, blastocysts were selected based on a minimum quality threshold defined by Gardner's grade (11), with BB or higher being the standard for freezing.

The study's results were reported in accordance with the STROBE guidelines.

Statistical analysis

Data in the study were processed using SPSS version 28.0 (IBM Corporation, Chicago, IL, USA). Data was assessed for normal distribution employing the Kolmogorov-Smirnov test and it was found that the continuous data was normally distributed. Baseline characteristics of the patients were then described using means, standard deviations, and ranges or percentages, as appropriate.

For the primary and secondary outcomes, t-tests were used for analysis, applying Levene's test to ensure equality of variances. Significance was determined with a two-tailed p-value, setting the threshold for statistical significance at less than 0.05.

Results

Our study included 82 patients who met the inclusion criteria. Of these, 43 were administered both FSH and LH activity, while the remaining 39 received only FSH. The baseline characteristics of both groups were comparable, with the notable exception of initial serum TSH levels. The group receiving only FSH exhibited higher pre-treatment serum TSH levels (average 3.6±8.3 mU/L) compared to the FSH and LH group (1.8±1.0 mU/L), a difference that closely approached significance (p=0.05). For participants with TSH levels above 3.5 mU/L, levothyroxine was administered to reduce serum TSH to below 2.0 mU/L prior to initiating the IVF cycle. Baseline characteristics are presented in Table 1.

There were no significant differences in several IVF outcomes between the FSH alone and FSH + LH groups. These outcomes included the pregnancy rates, clinical pregnancy rates, and live birth rates after the first embryo transfer, as well as the cumulative pregnancy rates.

Table 1. Patient baseline characteristics in the treatment groups

Variable	FSH and LH, (n=43)	FSH only, (n=39)	p
Gravidity	0.6±1.1	0.6±0.8	0.129
Parity	0.2±0.4	0.3±0.6	0.063
Female age (years)	30.8±2.8	30.2±3.6	0.345
Male age (years)	33.9±5.0	35.7±6.8	0.247
Duration of infertility (years)	3.0±2.2	3.3±2.5	0.607
Basal serum FSH (IU/mL)	6.1±1.7	5.5±1.5	0.980
Basal serum LH (IU/L)	9.4±6.7	7.8±5.2	0.454
Basal serum estradiol (pmol/L)	247.5±349.9	216.4±146.6	0.560
Basal serum prolactin (μg/L)	10.4±5.4	10.8±4.3	0.639
Basal serum TSH (mU/L)	1.8±1.0	3.6±8.2	0.05
Basal total serum testosterone (nmol/L)	1.9±1.2	1.4±0.7	0.098
Basal free serum testosterone (nmol/L)	0.8±0.6	0.6±0.4	0.212
AFC	45.9±1.3	44.6±17.3	0.856
Sperm volume (mL)	2.9±1.3	2.6±1.4	0.671
Sperm concentration (millions/mL)	44.8±39.2	35.7±32.3	0.265
Sperm motility (%)	44.3±23.7	38.2±30.2	0.038

Data are presented as mean ± standard deviation. FSH: Follicle-stimulating hormone, LH: Luteinizing hormone, TSH: Thyroid stimulating hormone, AFC: Antral follicle count

However, an interesting observation was the difference in cumulative live birth rate, which was higher in the FSH-only group (30 of 39, 76.9%) compared to the FSH + LH group (24 of 43, 55.8%), a difference that reached significance (p=0.044) (Table 2).

There were no significant differences in most stimulation outcomes. Specifically, peak serum estradiol, peak endometrial thickness, the number of oocytes collected, MII oocytes, 2PN embryos, and blastocysts frozen showed comparable results between the two groups (Table 3).

However, the FSH + LH group required a lower total dose of FSH (1271.5±376.7 vs. 1407.2±645.3 IU, p=0.02), had a shorter IVF cycle stimulation length (7.3±3.4 vs. 8.3±1.6 days, p=0.004), and had a higher number of follicles stimulated (36.9±15.9 vs. 35.9±9.7 p=0.008) compared to the FSH-only group (Table 3).

Discussion

In this study comparing IVF cycles among PCOS patients undergoing freeze-all GnRH antagonist protocols, no significant differences were found in initial and cumulative pregnancy rates, clinical pregnancy rates, and live birth rates between patients treated exclusively with FSH and those receiving a combination of FSH and exogenous LH. However, the cumulative live birth rate was higher in the FSH-only group compared to the combined FSH + LH group. The combined treatment group, however, required lower total doses of FSH, had shorter cycle durations, and achieved a higher number of stimulated follicles than the FSH-only group.

No significant differences were found in most measures, such as total oocytes collected, number of mature (MII) oocytes, fertilization rate, and embryos frozen. Similarly, primary outcomes, like cumulative pregnancy rates, first transfer pregnancy and clinical pregnancy rates, and live birth rates after the first transfer showed no statistical differences. However, cycle length and total follicles were notably different, with the FSH plus LH group showing advantages. This aligns with the known effect of LH on theca cells, stimulating small follicle growth (12,13). Despite more follicles, the addition of LH appeared to adversely affect oocyte quality, as suggested by lower cumulative live birth rates in this group. Previous studies have not directly compared rFSH alone versus rFSH with LH supplementation in GnRH antagonist cycles in PCOS patients. However, the effect of elevated basal LH/FSH ratios on IVF stimulation cycles has been explored. Singh et al. (7) conducted a retrospective cohort study examining the influence of high basal day 2 or 3 LH levels and LH:FSH ratio on IVF cycle outcomes in PCOS patients. They reviewed 164 cycles and found that those with lower basal LH levels showed higher fertilization rates and a greater number of fresh embryo transfers (7). Furthermore, Wang et al. (14) observed significant differences in cumulative clinical pregnancy rates

Table 2. Pregnancy outcomes

Variable	FSH and LH, (n=43)	FSH only, (n=39)	p
Pregnancy rate at the first transfer (%)	22 (51.2)	23 (59.0)	0.478
Clinical pregnancy rate after the first transfer (%)	16 (37.2)	18 (46.2)	0.412
Live birth rate following first transfer (%)	10 (23.3)	15 (38.5)	0.135
Cumulative clinical pregnancy rate (%)	32 (74.4)	33 (84.6)	0.441
Cumulative live birth rate (%)	24 (55.8)	30 (76.9)	0.044
FSH: Follicle-stimulating hormone, LH: Luteinizing hormone			

Table 3. Cycle characteristics and IVF stimulation outcomes

Variable	FSH and LH, (n=43)	FSH only, (n=39)	p
Cycle length (days of FSH stimulation)	7.3±3.4	8.3±1.6	0.004
Total dose of FSH (IU)	1407.2±645.3	1271.5±376.7	0.020
Peak serum estradiol (pmol/L)	13231±6859	11716±5086	0.220
Endometrial thickness (mm)	10.2±1.8	10.4±2.4	0.257
Total follicles stimulated (at least 10 mm)	36.9±15.9	35.9±9.7	0.008
Oocytes collected	27.0±9.4	28.4±9.7	0.837
Number of MII oocytes	20.0±7.9	21.6±8.2	0.861
Number of 2PN embryos	14.7±7.7	16.7±7.1	0.986
Number of embryos frozen	7.9±4.9	7.7±5.03	0.571
Data are presented as mean ± standard deviation. IVF: In-vitro fertilization, FSH: Follicle-stimulating hormone, LH: Luteinizing hormone, MII oocytes: Mature oocytes, 2PN: 2 pronuclei stage			

in PCOS patients undergoing GnRH antagonist IVF cycles, based on varying basal serum LH levels on the day of hCG trigger. Their study suggested that increasing LH levels during ovarian hyperstimulation could detrimentally affect pregnancy outcomes, possibly through adverse effects on oocytes, embryos, or the endometrium (14). Although baseline TSH levels were elevated in the FSH-only group, these levels were normalized before beginning the IVF cycle.

LH plays a crucial role in follicular recruitment, including stimulating FSH receptor expression in granulosa cells, facilitating follicular maturation, and promoting embryo implantation by affecting endometrial stromal cells (3). Its importance is evident in patients with hypogonadotropic hypogonadism (HH), where LH supplementation has shown benefits in ovarian stimulation. It has been found that HH patients treated with HMG, which contains LH activity, required lower FSH doses and achieved better ovulation rates and endometrial development compared to those treated with FSH alone (15). However, there is a balance to be maintained, as excessive LH activity can lead to premature follicular maturation and atresia. High serum LH levels during the follicular phase are associated with poorer oocyte quality, reduced fertilization rates, impaired embryo implantation, and increased miscarriage risks (16). This may explain the higher cumulative live birth rate that was observed in the FSH-only group.

Previous studies (12,17) have explored ovarian stimulation protocols in non-PCOS subjects, but the present study is unique in its focus on PCOS patients under GnRH antagonist protocols. Furthermore, it is important to acknowledge the distinct effects of long GnRH agonist and GnRH antagonist protocols on endogenous LH levels in IVF. Long GnRH agonist cycles typically lead to a significant reduction in serum LH levels in PCOS patients, potentially extending over three to four weeks, starting from pre-stimulation. In contrast, GnRH antagonist protocols cause a more transient suppression of LH, often lasting only a few days (18,19). This difference in LH dynamics may result in varying IVF outcomes, especially for PCOS patients. The rationale for using GnRH antagonist protocols, for reducing ovarian hyperstimulation syndrome risk, is well-established (20). The results of the present study suggest that LH supplementation may have varying effects in PCOS patients, who naturally exhibit elevated endogenous LH levels. These levels could be further amplified in patients undergoing GnRH antagonist protocols, underscoring the need for careful consideration of LH supplementation in this specific patient group.

The higher cumulative live birth rate observed in the FSH only group, as opposed to the FSH with LH activity group, could be attributed to the exclusive focus on PCOS patients. Elevated LH concentrations in these patients may negatively impact oocyte quality, as inferred from live birth potential. Furthermore, patients with high basal LH levels are likely to exhibit elevated progesterone levels on IVF trigger days, potentially affecting oocyte potential, even in frozen cycles (7).

Study limitations

The findings of this study are innovative, yet they are subject to certain limitations that warrant attention. The retrospective design and limited sample size could introduce confounding factors, possibly affecting the interpretability of the results. A larger sample might reveal statistical significance in cumulative pregnancy rate and other primary outcomes. Nevertheless, the observed clinical outcomes are significant enough to merit reporting. Due to the scale of the study, it should primarily serve as a basis for hypothesis generation, with further validation required from larger-scale studies. While we inferred improved oocyte quality from better clinical outcomes, this was not directly measured. In addition, the impact of the timing of exogenous LH addition, which in this study coincided with FSH stimulation, may influence oocyte maturation and clinical results. Different outcomes might have been observed if LH stimulation had been administered only during the late follicular phase.

Conclusion

This study found that for PCOS patients undergoing GnRH antagonist IVF “freeze-all” protocols, ovarian stimulation with FSH and LH resulted in comparable clinical pregnancy and live birth rates to using FSH alone. However, FSH and LH stimulation allowed for reduced FSH dosages, a shorter duration of IVF stimulation, and an increased number of stimulated follicles, when compared to FSH alone. Despite these benefits, the cumulative live birth rate was lower with FSH and LH stimulation when compared to treatment with FSH only.

Ethics Committee Approval: *The study was submitted and approved by the board of the McGill University Research Ethics Office (Internal Review Board) of the Faculty of Medicine and Health Sciences (approval number: 2020-5971).*

Informed Consent: *Retrospective study.*

Author Contributions: *Surgical and Medical Practices: N.K., A.P., M.H.D.; Concept: N.K., A.P., M.H.D.; Design: N.K., A.P., M.H.D.; Data Collection or Processing: N.K., A.P., K.R.O., V.B., A.D.; Analysis or Interpretation: N.K., A.P., K.R.O., V.B., A.D.; Literature Search: N.K., A.P.; Writing: N.K., A.P., K.R.O., V.B., A.D., M.H.D.*

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