Basal serum luteinizing hormone, total testosterone, and free testosterone levels do not impact IVF outcomes in patients with polycystic ovary syndrome

Nir Kugelman[1,2*], Alyson Digby[1*], Keren Rotshenker-Olshinka[1,3], Véronique Bellemare[1], Amrita Pooni[1], Weon-Young Son[1], Michael H Dahan[1]

[1]Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology and Infertility, McGill University, Montreal, Canada

[2]Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

[3]Department of Obstetrics and Gynecology, Hebrew University, Shaare Zedek Medical Center, Jerusalem, Israel

*The first two authors had equal contribution

Abstract

Objective: To assess the influence of basal serum levels of luteinizing hormone (LH), total testosterone (TT), and free testosterone (FT) on in vitro fertilization (IVF) success rates in patients with polycystic ovary syndrome (PCOS).

Material and Methods: A retrospective cohort analysis of PCOS patients who underwent freeze-all, gonadotropin releasing hormone (GnRH) antagonist IVF protocols from January 2013 to December 2019. Patients were grouped based on median basal serum levels of LH, TT, and FT to compare their IVF outcomes.

Results: A total of 76 women with PCOS diagnosed as per the 2003 Rotterdam criteria were included. When analyzed by LH levels, groups had similar baseline characteristics except for higher mean ± standard deviation TT (1.4±0.9 vs. 1.9±0.9 nmol/L, p=0.02) and FT (0.6±0.5 vs. 0.9±0.5 nmol/L, p=0.03) in the elevated LH group. However, clinical pregnancy rates (CPR) (34.2% vs. 44.7%, p=0.35) and live birth rates (LBR) (21.0% vs. 31.6%, p=0.29) were not different. The group with lower TT had more previous pregnancies (0.9±1.2 vs. 0.3±0.7, p=0.02) and shorter infertility duration (2.3±2.0 vs. 3.7±2.7 years, p=0.04), but again CPR (46.8% vs. 42.8%, p=0.90) and LBR (37.5% vs. 25.7%, p=0.33) were similar. FT analysis revealed no significant differences in CPR (48.2% vs. 36.7%, p=0.36) and LBR (23.2% vs. 37.9%, p=0.22) despite higher TT (1.1±0.4 vs. 2.2±1.1 nmol/L, p<0.001) and LH (6.1±3.8 vs. 11.2±7.2 IU/L, p<0.001) in the high FT group.

Conclusion: Basal serum levels of LH, TT, and FT did not significantly affect IVF outcomes in patients with PCOS using GnRH antagonist, freeze-all protocols. (J Turk Ger Gynecol Assoc. 2024; 25: 192-9)

Keywords: Polycystic ovary syndrome, in vitro fertilization, luteinizing hormone, total testosterone, free testosterone

Received: 16 July, 2024 **Accepted:** 11 October, 2024

Introduction

The correlation between initial serum levels of luteinizing hormone (LH), total testosterone (TT), and free testosterone (FT) and in vitro fertilization (IVF) outcomes remains a contentious issue (1). Women with polycystic ovary syndrome (PCOS) often exhibit increased amplitude and frequency of LH secretion (2). Given that PCOS is a predominant contributor to infertility through its disruption of ovulation, understanding the impact of these hormone variations is important in clinical practice (3). Many IVF centers delay ovarian stimulation until early follicular phase basal levels of LH, TT, or FT are reduced, based on concerns that elevated levels might negatively influence miscarriage rates, oocyte quality and quantity, and

Address for Correspondence: *Nir Kugelman*
e.mail: e.mail: nirkug@gmail.com ORCID: orcid.org/0000-0002-2473-7408
DOI: 10.4274/jtgga.galenos.2024.2024-2-9

overall pregnancy success (4-7). However, some studies suggest that high basal LH levels may not compromise IVF outcomes (8).

The rationale for delaying stimulation based on basal hormone levels is the expectation of better outcomes in subsequent cycles. However, significant hormonal fluctuations mean a single measurement will not accurately represent a patient's hormonal profile (9). In addition, previous research was conducted before the widespread adoption of gonadotropin releasing hormone (GnRH) antagonist protocols for PCOS, which minimize the risk of ovarian hyperstimulation syndrome (OHSS) (10). Recent but limited research has suggested that hormone level variations may be temporary and less critical to pregnancy outcomes than previously thought. The present study assessed how initial serum concentrations of LH, TT, and FT affect IVF success rates in women with PCOS.

Material and Methods

This study was a retrospective cohort analysis performed at a university-affiliated fertility center, using electronic medical records collected from January 1, 2013, to December 31, 2019. The study protocol received approval from the McGill University Health Centre Institutional Review Board Ethics Committee (approval number: REB 2020-5971, date: 31.10.2019), and informed consent was waived owing to the study's retrospective design.

The study included women diagnosed with PCOS who participated in freeze-all GnRH antagonist IVF treatments. Participants were categorized into two groups depending on whether their basal serum levels of LH, TT, and FT, measured between days 2 and 5 of a natural or progestin-induced cycle, fell above or below the median. Each participant's PCOS diagnosis was confirmed via chart review following the Rotterdam criteria (11). Individual subjects were only included once in this study.

Inclusion criteria were patients who had undergone a GnRH antagonist IVF cycle with all embryos cryopreserved, followed by a frozen embryo transfer, and a confirmed PCOS diagnosis. Exclusion criteria included patients with untreated uterine pathologies, such as intra-cavitary polyps, fibroids, or ultrasound-visible hydrosalpinxes, and individuals with severe male infertility necessitating surgical sperm retrieval. Additionally, to exclude non-classical congenital adrenal hyperplasia, only patients with 17-hydroxyprogesterone levels below 2 ng/mL were included in the study, ensuring that all participants were within the normal range for women of reproductive age. Serum dehydroepiandrosterone sulfate levels were also measured to rule out an androgen secreting adrenal tumor. However, these results were not measured close to the IVF cycle and as such could not be compared in this study. They were often performed one or more years before care was initiated.

Demographic and baseline characteristics collected included female age, duration of infertility, gravidity, parity, serum estradiol, basal follicle-stimulating hormone (FSH), thyroid-stimulating hormone (TSH), prolactin, TT, FT, antral follicle count (AFC), male age, and semen analysis. The primary outcomes were clinical pregnancy rates (CPR) and live birth rates (LBR). Secondary outcomes included the total number of oocytes retrieved, the number of mature (MII) oocytes, the number of embryos reaching the two pronuclei (2PN) stage, the total number of blastocysts cryopreserved, and miscarriage rates.

A fixed antagonist protocol was used, initiating gonadotropins on the third day of the menstrual cycle, whether spontaneous or progestin induced. Experienced sonographers conducted baseline ultrasounds during the early follicular phase to check for anatomical abnormalities (such as fibroids, adenomyosis, ovarian cysts, and signs of endometriosis) and determine the AFC. GnRH antagonist treatment, using either Orgalutran (Organon, Canada) or Cetrotide (Merck Serono, Canada), began on the sixth day of gonadotropin therapy. Ovarian stimulation was performed using recombinant FSH alpha (Merck Serono Canada), recombinant FSH beta (Organon, Canada), or menopausal gonadotropins (Ferring, Canada). The ovulation trigger primarily involved Buserelin (Suprefact, Sanofi-Aventis, Canada), with some patients receiving recombinant beta-human chorionic gonadotropin (β-hCG) 250 mcg subcutaneously (Ovidrel, Serono, Canada). Egg collection was executed 36 hours following the ovulation trigger. Fertilization was performed either through conventional IVF or intracytoplasmic sperm injection (ICSI), with fertilization assessments conducted 16-18 hours post-retrieval. ICSI was performed primarily in cases of poor motility (<30%), oligospermia, abnormal strict morphology, and after unsuccessful fertilization in previous IVF attempts without ICSI. Due to the risk of OHSS, all embryos were cryopreserved. Only embryos graded 3BB or higher according to Gardner's criteria (12) were frozen at the blastocyst stage.

Future research should focus on the impact of peri-trigger serum progesterone levels on IVF outcomes in patients with PCOS. Moreover, further studies should investigate the stimulation-induced production of hormones such as LH and testosterone, and their subsequent influence on IVF outcomes. Pregnancy was confirmed by a serum β-hCG level of ≥20 IU/L sixteen days after transfer. Clinical pregnancy was confirmed by the presence of an intrauterine gestational sac with a fetal pole and heartbeat observed through transvaginal ultrasound between 6 and 7 weeks. Miscarriage was defined as the spontaneous loss of a pregnancy before 20 weeks of gestation, including

biochemical pregnancies, which were characterized by a positive pregnancy test but no clinical evidence of a gestational sac on ultrasound. Live birth was defined as the birth of a live infant after 20 weeks of gestation.

Statistical analysis

SPSS, version 23.0 (IBM Inc., Armonk, NY, USA) was used. Participants were categorized into two groups based on their serum LH levels: the lower 50% (1.0-7.0 IU/L) and the higher 50% (7.1-29.0 IU/L). A similar classification was applied to serum TT levels (0.30-1.50 nmol/L vs. 1.6-5.6 nmol/L) and FT levels (0.07-0.50 nmol/L vs. 0.51-2.70 nmol/L). Comparisons between the two groups for each serum marker were performed using independent t-tests for continuous variables and chi-squared tests for categorical variables. A p-value <0.05 was deemed statistically significant.

Results

Over the study period, 76 women meeting the inclusion criteria were identified. Analysis based on basal serum LH levels showed no significant differences in baseline characteristics between groups, except for mean ± standard deviation (SD) TT levels (1.4±0.9 vs. 1.9±0.9 nmol/L, p=0.02) and FT levels (0.6±0.5 vs. 0.9±0.5 nmol/L, p=0.03), which were higher in the elevated LH group (Table 1). The mean ± SD counts for oocytes retrieved (26.8±7.4 vs. 27.3±9.6, p=0.82), mature MII oocytes (19.9±6.8 vs. 20.2±7.8, p=0.88), and cryopreserved high-quality blastocysts (6.9±4.4 vs. 8.2±5.1, p=0.25) showed no significant differences between the groups. Similarly, the fertilization rate of MII oocytes (75.1±16.2% vs. 73.9±18.8%, p=0.78), the percentage of 2PN embryos developing into blastocysts (47.4±23.0% vs. 55.0±27.0%, p=0.18), and the proportion of MII oocytes progressing to blastocysts (34.9±18.0% vs. 39.8±18.8%, p=0.25) were comparable. Following embryo transfer, CPR (34.2% vs. 44.7%, p=0.35) and LBR (21.0% vs. 31.6%, p=0.29) were not significantly different between the groups. Miscarriage rates were found to be 52% in the lower LH group and 39% in the higher LH group, with no statistically significant difference between the groups (p=0.40) (Table 2).

When examining baseline characteristics based on TT levels, the lower TT group had a greater mean ± SD number of prior pregnancies (0.9±1.2 vs. 0.3±0.7, p=0.02), a shorter duration of infertility (2.3±2.0 vs. 3.7±2.7 years, p=0.04), and lower TSH (1.7±0.9 vs. 2.4±1.9 nmol/L, p=0.04) (Table 3). The counts of collected oocytes (27.5±7.5 vs. 28.3±9.7, p=0.73), mature MII oocytes (20.5±6.9 vs. 20.4±8.3, p=0.98), and cryopreserved

Table 1. Baseline characteristics of PCOS patients categorized by luteinizing hormone levels: upper 50% (7.1-29.0 IU/L) vs. lower 50% (1.0-7.0 IU/L)

Variable	Lower 50% LH, (n=38)	Upper 50% LH, (n=38)	p-value
Female age (years)	29.9±3.7	30.9±2.7	0.21
Duration of infertility (years)	3.2±2.6	3.0±2.1	0.82
Parity	0.2±0.5	0.2±0.5	0.82
Gravidity	0.7±0.9	0.6±1.1	0.65
Baseline FSH (IU/L)	5.4±1.5	5.9±1.3	0.15
Baseline LH (IU/L)	4.2±1.4	13.0±5.7	0.001
Baseline estradiol (pmol/L)	193.6±121.3	277.6±364.2	0.20
Prolactin (mcg/L)	10.0±3.5	10.7±5.6	0.50
TSH (mIU/L)	2.2±1.8	3.3±8.2	0.40
Total testosterone (nmol/L)	1.4±0.9	1.9±0.9	0.02
Free testosterone (nmol/L)	0.6±0.5	0.9±0.5	0.03
Antral follicle count	42.3±15.2	50.9±22.6	0.09
Male age (years)	33.7±5.6	34.7±4.9	0.46
Sperm concentration (mil/mL)	38.8±32.3	41.4±36.9	0.75
Ejaculate volume (mL)	2.6±1.2	2.7±1.3	0.61
Semen motility (%)	40.1±26.6	44.9±27.6	0.46
Total motile sperm count (Mil)	53.4±77.7	75.1±97.7	0.31
FSH total dose (IU)	1287.1±518.4	1311.2±458.5	0.84
Peak estradiol during stimulation (nmol/L)	10980.1±4760.9	13982.7±6613.4	0.03
Peak endometrial thickness (mm)	10.1±2.0	10.3±2.1	0.81

Data are presented as mean ± standard deviation, PCOS: Polycystic ovary syndrome, LH: Luteinizing hormone, FSH: Follicle-stimulating hormone, TSH: Thyroid stimulating hormone

Table 2. Embryologic and pregnancy outcomes of PCOS patients categorized by luteinizing hormone levels: upper 50% (7.1-29.0 IU/L) vs. lower 50% (1.0-7.0 IU/L)

Variable	Lower 50% LH, (n=38)	Upper 50% LH, (n=38)	p-value
Number of oocytes collected	26.8±7.4	27.3±9.6	0.82
Number of MII oocytes	19.9±6.8	20.2±7.8	0.88
MII fertilized (%)	75.1±16.2	73.9±18.8	0.78
2PN grew to blastocyst (%)	47.4±23.0	55.0%±27.0	0.18
MII grew to blastocyst (%)	34.9±18.0	39.8±18.8	0.25
Number of embryos frozen	6.9±4.4	8.24±5.1	0.25
Clinical pregnancy no. (%)	13 (34.2)	17 (44.7)	0.35
Miscarriage no/total pregnancies (%)	12/23 (52%)	7/18 (39%)	0.40
Live birth no. (%)	8 (21.0)	12 (31.6)	0.29

Data are presented as mean ± standard deviation, PCOS: Polycystic ovary syndrome, LH: Luteinizing hormone, MII oocytes: Mature oocytes, 2PN: 2 pronuclei stage

Table 3. Baseline characteristics of PCOS patients by total testosterone levels: upper 50% (1.6-5.6 nmol/L) vs. lower 50% (0.30-1.50 nmol/L)

Variable	Lower 50% TT, (n=32)	Upper 50% TT, (n=35)	p-value
Female age (years)	30.1±3.2	30.8±3.3	0.37
Duration of infertility (years)	2.3±2.0	3.7±2.7	0.04
Parity	0.3±0.6	0.1±0.4	0.11
Gravidity	0.9±1.2	0.3±0.7	0.02
Baseline FSH (IU/L)	5.7±1.1	5.6±1.6	0.78
Baseline LH (IU/L)	6.9±5.2	10.0±6.8	0.04
Baseline estradiol (pmol/L)	168.6±82.4	302.0±377.7	0.06
Prolactin (mcg/L)	10.0±3.1	10.4±5.5	0.70
TSH (mIU/L)	1.7±0.9	2.4±1.9	0.04
Total testosterone (nmol/L)	0.9±0.4	2.3±0.9	0.001
Antral follicle count	45.6±22.7	48.9±17.7	0.53
Male age (years)	34.5±5.4	33.9±4.6	0.68
Sperm concentration (mil/mL)	35.0±28.3	46.1±44.0	0.24
Ejaculate volume (mLl)	2.9±1.2	2.4±1.2	0.12
Semen motility (%)	39.1±29.3	44.9±30.2	0.41
Total motile sperm count (Mil)	58.7±76.3	77.3±119.9	0.47
FSH total dose (IU)	1199.5±424.4	1402.1±552.2	0.11
Peak estradiol during stimulation (nmol/L)	11561.9±3802.5	13318.9±7716.2	0.24
Peak endometrial thickness (mm)	10.1±2.2	10.3±1.9	0.69

Data are presented as mean ± standard deviation, PCOS: Polycystic ovary syndrome, TT: Total testosterone, FSH: Follicle-stimulating hormone, LH: Luteinizing hormone, TSH: Thyroid stimulating hormone

high-quality blastocysts (6.9±4.0 vs. 8.1±5.7, p=0.32) showed no significant differences between the groups. Furthermore, the fertilization rate of MII oocytes (73.3±18.8% vs. 73.5±16.7%, p=0.96), the percentage of 2PN embryos developing into blastocysts (48.3±22.9% vs. 52.5±27.5%, p=0.50), and the proportion of MII oocytes advancing to the blastocyst stage (34.1±17.0% vs. 38.2±19.1%, p=0.36) were similar. CPR (46.8% vs. 42.8%, p=0.90) and LBR (37.5% vs. 25.7%, p=0.33) did not significantly differ among patients who underwent embryo transfer. Miscarriage rates in the lower and upper TT groups were 45% and 50%, respectively (p=0.77) (Table 4).

The impact of FT levels on IVF outcomes in PCOS patients was also evaluated. Significant differences in baseline characteristics were observed for serum TT (1.1±0.4 vs. 2.2±1.1 nmol/L, p<0.001) and serum LH levels (6.1±3.8 vs. 11.2±7.2 IU/L, p<0.001) (Table 5). The counts of retrieved

Table 4. Embryologic and pregnancy outcomes of PCOS patients by total testosterone levels: upper 50% (1.6-5.6 nmol/L) vs. lower 50% (0.30-1.50 nmol/L)

Variable	Lower 50% TT, (n=32)	Upper 50% TT, (n=35)	p-value
Number of oocytes collected	27.5±7.5	28.3±9.7	0.73
Number of MII oocytes	20.5±6.9	20.4 3±8.3	0.98
MII fertilized (%)	73.3±18.8	73.5±16.7	0.96
2PN grew to blastocyst (%)	48.3±22.9	52.5±27.5	0.50
MII grew to blastocyst (%)	34.1±17.0	38.2±19.1	0.36
Number of embryos frozen	6.9±4.0	8.1±5.7	0.32
Clinical pregnancy no. (%)	15 (46.8)	15 (42.8)	0.90
Miscarriage no/total pregnancies (%)	10/22 (45%)	9/18 (50%)	0.77
Live birth no. (%)	12 (37.5)	9 (25.7)	0.33
Data are presented as mean ± standard deviation, PCOS: Polycystic ovary syndrome, TT: Total testosterone, LH: Luteinizing hormone, MII oocytes: Mature oocytes, 2PN: 2 pronuclei stage			

Table 5. Baseline characteristics of PCOS patients by free testosterone levels: upper 50% (0.51 to 2.70 nmol/L) vs. lower 50% (0.07-0.50 nmol/L)

Variable	Lower 50% FT, (n=29)	Upper 50% FT, (n=30)	p-value
Female age (years)	30.4±3.3	30.4±3.5	0.99
Duration of infertility (years)	2.4±1.9	3.6±2.5	0.66
Parity	0.2±0.6	0.1±0.4	0.41
Gravidity	0.6±0.9	0.6±1.1	0.84
Baseline FSH (IU/L)	5.7±1.3	5.8±1.5	0.73
Baseline LH (IU/L)	6.1±3.8	11.2±7.2	<0.001
Baseline estradiol (pmol/L)	176.0±81.8	283.3±389.5	0.19
Prolactin (mcg/L)	10.0±3.2	10.7±5.6	0.56
TSH (mIU/L)	1.8±1.1	2.2±2.0	0.33
Total testosterone (nmol/L)	1.1±0.4	2.2±1.1	<0.001
Antral follicle count	43.6±18.2	54.5±20.9	0.06
Male age (years)	33.4±4.7	34.8±5.8	0.30
Sperm concentration (mil/mL)	38.6±33.7	43.2±40.2	0.64
Ejaculate volume (mL)	2.7±1.4	2.9±1.5	0.50
Semen motility (%)	34.6±26.2	43.7±26.0	0.054
Total motile sperm count (Mil)	51.4±86.2	67.6±107.8	0.36
FSH total dose (IU)	1235.7±491.9	1391.6±520.4	0.26
Peak estradiol during stimulation (nmol/L)	12397.5±4123.0	13680.9±7805.8	0.44
Peak endometrial thickness (mm)	10.3±2.5	10.4±1.6	0.81
Data are presented as mean ± standard deviation, PCOS: Polycystic ovary syndrome, FT: Free testosterone, FSH: Follicle-stimulating hormone, LH: Luteinizing hormone, TSH: Thyroid stimulating hormone			

oocytes (26.3±7.4 vs. 29.8±8.7, p=0.10), mature MII oocytes (19.9±6.0 vs. 21.3±9.0, p=0.50), and cryopreserved high-quality blastocysts (7.0±4.3 vs. 8.4±6.0, p=0.30) did not differ between groups. The fertilization rate of MII oocytes (75±17% vs. 73±19%, p=0.42), the percentage of 2PN embryos developing into blastocysts (49±19% vs. 51±24%, p=0.63), and the proportion of MII oocytes advancing to the blastocyst stage (37±17% vs. 36±16%, p=0.77) were comparable. Once more the CPR (48.2% vs. 36.7%, p=0.36) and LBR (23.2% vs. 37.9%, p=0.22) did not significantly differ in patients who underwent embryo transfer. Miscarriage rates were 58% in the lower FT group compared to 68% in the higher FT group (p=0.45) (Table 6).

Table 6. Embryologic and pregnancy outcomes of PCOS patients by free testosterone levels: upper 50% (0.51 to 2.70 nmol/L) vs. lower 50% (0.07-0.50 nmol/L)

Variable	Lower 50% FT, (n=29)	Upper 50% FT, (n=30)	p-value
Number of oocytes collected	26.3±7.4	29.8±8.7	0.10
Number of MII oocytes	19.9±6.0	21.3±9.0	0.50
MII Fertilized (%)	75±17	73±19	0.42
2PN grew to blastocyst (%)	49±19	51±24	0.63
MII grew to blastocyst (%)	37±17	36±16	0.77
Number of embryos frozen	7.00±4.3	8.40±6.0	0.30
Clinical pregnancy no. (%)	14 (48.2)	11 (36.7)	0.36
Miscarriage no/total pregnancies (%)	15/26 (58)	15/22 (68)	0.45
Live birth no. (%)	11 (37.9)	7 (23.3)	0.22
Data are presented as mean ± standard deviation, FT: Free testosterone, LH: Luteinizing hormone, MII oocytes: Mature oocytes, 2PN: 2 pronuclei stage			

Discussion

The aim of this study was to assess if elevated basal serum levels of LH, TT, and FT influenced outcomes in freeze-all, GnRH-antagonist IVF cycles for patients with PCOS. The results revealed no significant differences in CPR, LBR, or IVF stimulation outcomes across varying hormonal levels. Notably, patients in the elevated basal serum LH group had higher TT and FT levels. Analysis of TT groups showed differences in baseline characteristics and clinical parameters such as serum TSH levels, duration of infertility, and prior pregnancies, but these did not impact overall success rates. Similar trends were observed within the FT groups, which were mainly distinguished by their higher basal serum TT and LH levels without impacting key treatment outcomes.

Earlier research primarily focused on PCOS patients undergoing IVF before the common use of freeze-all, GnRH-antagonist protocols. Many clinics have used basal serum LH values on day 3 of the menstrual cycle to decide on cycle cancellations, as reported in previous studies (8,13). However, these studies may not be relevant to current practice with changes in management. Recent research, such as the study by Singh et al. (1), presents different findings, likely due to advances in GnRH-antagonist protocols and frozen-embryo transfer cycles. Unlike Singh et al.'s (1) study, the present study included only frozen embryo transfers, limiting our outcomes to the effects on oocyte and embryo potential. A recent randomized controlled trial by Chen et al. (14) demonstrated that PCOS patients undergoing frozen embryo transfer experienced higher live birth rates and a reduced risk of OHSS compared to those receiving fresh embryo transfers.

The higher peak estradiol levels in the higher LH group likely indicate stronger follicular activity. However, this did not translate into significantly different clinical outcomes, such as the number of oocytes retrieved, fertilization rate, embryo quality, CPR, miscarriage rate, or live birth rate. This observation is consistent with other studies suggesting that while estradiol levels are indicative of follicular activity, they may not directly correlate with pregnancy success in PCOS patients (15,16).

The pulsatile nature of LH means that a single measurement may not accurately represent an individual's hormonal status. In PCOS patients, LH levels are generally higher with an accelerated pulse frequency compared to normal controls. However, at any given time, these patients' serum LH levels could be low, normal, or high, depending on the steroid pulse curve (17). This variability highlights the lack of reliability in using single LH measurements to categorize hormonal status. PCOS patients often exhibit significant variability in hormonal levels due to the pulsatile nature of hormone secretion. This variability suggests that a single measurement may not capture the hormonal environment and may lead to misinterpretation of the hormonal status. This is particularly relevant for LH, where levels can fluctuate widely within a short period (18,19).

Freeze-all cycles create a separation between basal serum levels of LH, TT, and FT and the endometrial environment at the time of embryo transfer. While elevated serum LH is known to alter the ovarian hormonal environment (20), the impact of basal serum levels of LH, TT, and FT on fresh embryo transfer success remains unexplored, and is thus an important area for future research. Nevertheless, our findings suggest that ovarian stimulation outcomes, oocyte quality, and embryo development do not significantly differ across groups categorized by basal serum levels of LH, TT, or FT. This indicates that while hormonal levels may vary, their influence on core aspects of IVF treatment, such as stimulation response, oocyte, and embryo development, remains consistent regardless of basal hormone levels.

Study limitations

This study is subject to limitations inherent in a retrospective cohort design, including the reliance on previously documented data and the inability to control for various confounding factors, which may introduce potential biases and influence the generalizability of our findings. The accuracy and completeness of the information are particularly limited concerning factors such as anti-Mullerian hormone (AMH) levels, which were not performed at our institution until more recently due to high cost, and body mass index (BMI), which was not reliably recorded during the study period. The absence of AMH levels, an important marker for ovarian reserve and PCOS, restricts our ability to fully assess PCOS status. Similarly, the lack of accurate BMI data impedes a comprehensive analysis of the impact of body weight in PCOS on IVF outcomes. Moreover, there was insufficient data on complications, such as obstetrical outcomes, including pre-eclampsia, preterm birth, and placental pathology. Peri-trigger serum progesterone levels, which might influence several examined outcomes, were not routinely measured during the IVF process in our clinic. This could represent a potential confounding factor. Furthermore, the small sample size limits our ability to conclusively identify differences, and outcomes may have varied if fresh embryo transfers had been included. This study did not account for variations in stimulation protocols within the same patients, which could provide more insight into the consistency of hormonal impacts on IVF outcomes. Longitudinal studies are recommended to explore this aspect.

Future research should focus on the impact of peri-trigger serum progesterone levels on IVF outcomes in patients with PCOS. In addition, further studies should investigate the stimulation-induced production of hormones, including LH and testosterone, and their subsequent influence on IVF outcomes.

Conclusion

In PCOS patients undergoing freeze-all, GnRH antagonist IVF and frozen embryo transfer, basal serum levels of LH, TT, and FT did not show significant differences in oocyte/embryo quality, CPR, or LBR. This suggests that cancelling cycles for women with PCOS and high basal LH and testosterone levels, in anticipation of improved outcomes in future cycles, may not be necessary for those undergoing frozen embryo transfers.

Ethics Committee Approval: *The study protocol received approval from the McGill University Health Centre Institutional Review Board Ethics Committee (approval number: REB 2020-5971, date: 31.10.2019).*

Informed Consent: *Informed consent was waived owing to the study's retrospective design.*

Footnotes

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

Conflict of Interest: *No conflict of interest is declared by the authors.*

Financial Disclosure: *The authors declared that this study received no financial support.*

References

1. Singh N, Mishra N, Dogra Y. Do basal luteinizing hormone and luteinizing hormone/follicle-stimulating hormone ratio have significance in prognosticating the outcome of in vitro fertilization cycles in polycystic ovary syndrome? J Hum Reprod Sci. 2021; 14: 21-7.
2. Coutinho EA, Kauffman AS. The role of the brain in the pathogenesis and physiology of polycystic ovary syndrome (PCOS). Med Sci (Basel). 2019; 7: 84.
3. Zehravi M, Maqbool M, Ara I. Polycystic ovary syndrome and infertility: an update. Int J Adolesc Med Health. 2021; 34: 1-9.
4. Wang J, Ding J, Qu B, Zhang Y, Zhou Q. Does serum LH level influence IVF outcomes in women with PCOS undergoing GnRH-antagonist stimulation: a novel indicator. J Clin Med. 2022; 11: 4670.
5. Eini F, Kutenaei MA, Foroutan T, Salehi E. High levels of follicular fluid testosterone could impair oocyte developmental competency via affecting aryl hydrocarbon receptor pathway in PCOS patients. BMC Mol and Cell Biol. 2022; 23: 47.
6. Bansal S, Singh N, Gupta P, Malhotra N, Mahendru R. Does basal luteinizing hormone help predict the fate of in vitro fertilization? JBRA Assist Reprod. 2016; 20: 66-71.
7. De Vos M, Pareyn S, Drakopoulos P, Raimundo JM, Anckaert E, Santos-Ribeiro S, et al. Cumulative live birth rates after IVF in patients with polycystic ovaries: phenotype matters. Reprod Biomed Online. 2018; 37: 163-71.
8. Sun L, Ye J, Wang Y, Chen Q, Cai R, Fu Y, et al. Elevated basal luteinizing hormone does not impair the outcome of human menopausal gonadotropin and medroxyprogesterone acetate treatment cycles. Sci Rep. 2018; 8: 13835.
9. Greenwell S, Faskowitz J, Pritschet L, Santander T, Jacobs EG, Betzel RF. High-amplitude network co-fluctuations linked to variation in hormone concentrations over the menstrual cycle. Netw Neurosci. 2023; 7: 1181-205.
10. Palomba S, Costanzi F, Nelson SM, Caserta D, Humaidan P. Interventions to prevent or reduce the incidence and severity of ovarian hyperstimulation syndrome: a systematic umbrella review of the best clinical evidence. Reprod Biol Endocrinol. 2023; 21: 67.
11. Teede HJ, Tay CT, Laven JJE, Dokras A, Moran LJ, Piltonen TT, et al.; International PCOS Network. Recommendations from the 2023 international evidence-based guideline for the assessment and management of polycystic ovary syndrome. Eur J Endocrinol. 2023; 189: G43-64.

12. Kemper JM, Liu Y, Afnan M, Hammond ER, Morbeck DE, Mol BWJ. Should we look for a low-grade threshold for blastocyst transfer? A scoping review. Reprod Biomed Online. 2021; 42: 709-16.
13. Liu Z, Wang KH. Effect of basal luteinizing hormone (bLH) level on in vitro fertilization/intra-cytoplasmic injections (IVF/ICSI) outcomes in polycystic ovarian syndrome (PCOS) patients. BMC Pregnancy Childbirth. 2023; 23: 618.
14. Chen ZJ, Shi Y, Sun Y, Zhang B, Liang X, Cao Y, et al. Fresh versus frozen embryos for infertility in the polycystic ovary syndrome. N Engl J Med. 2016; 375: 523-33.
15. Zavy MT, Craig LB, Wild RA, Kahn SN, O'Leary D, Hansen KR. In high responding patients undergoing an initial IVF cycle, elevated estradiol on the day of hCG has no effect on live birth rate. Reprod Biol Endocrinol. 2014; 12: 119.
16. Wei CX, Zhang L, Pang CH, Qi YH, Zhang JW. Effect of the ratios of estradiol increase on the outcome of in vitro fertilization-embryo transfer with antagonist regimens: a single center retrospective cohort study. BMC Pregnancy Childbirth. 2023; 23: 134.
17. Taylor HS, Pal L, Seli E. Chronic anovulation and the polycystic ovary syndrome. In: Speroff's Clinical Gynecologic Endocrinology and Infertility. 9th ed. Wolters Kluwer: India; 2019. p. 395-441.
18. Marshall JC, Dunaif A. Should all women with PCOS be treated for insulin resistance? Fertil Steril. 2012; 97: 18-22.
19. Waldstreicher J, Santoro NF, Hall JE, Filicori M, Crowley WF Jr. Hyperfunction of the hypothalamic-pituitary axis in women with polycystic ovarian disease: indirect evidence for partial gonadotroph desensitization. J Clin Endocrinol Metab. 1988; 66: 165-72.
20. Dragotto J, Buzzaccarini G, Etrusco A, Laganà AS, Venezia R, Terzic S, et al. Effects of low luteinizing hormone serum levels on oocyte retrieval, fertilization rate, and embryo quality during controlled ovarian stimulation: results from a prospective cohort analysis. Gynecol Obstet Invest. 2024; 89: 50-8.