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Role of LH level on ICSI outcome in women with PCOS Undergoing GnRh antagonist stimulation

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Abstract
Background: Polycystic Ovary Syndrome (PCOS) impairs fertility through hyperandrogenemia, insulin resistance, and elevated LH/FSH ratios, affecting oocyte quality and implantation. This study investigates the impact of serum LH levels on IVF/ICSI outcomes, including pregnancy and live birth rates. Aim of study is to Explore the Influence of LH Levels on IVF/ICSI Outcomes in Women with PCOS Undergoing GnRH-Antagonist Stimulation Protocol.
Methods: Ninety IVF/ICSI patients with PCOS undergoing GnRH-antagonist protocols were divided into groups based on basal LH (bLH), trigger-day LH (hLH), and hLH/bLH ratio. Relationships between LH levels and outcomes like oocytes retrieved, pregnancy rates, and live birth rates were analyzed. Secondary factors included fertilization rates, top-quality embryos, and total Gn dose.
Results: No significant differences were found among groups based on bLH levels, but lower hLH (≤2 mIU/mL) was associated with reduced basal FSH and LH levels. Patients with hLH/bLH ≤ 0.5 had higher clinical pregnancy rates, while those with hLH/bLH ≥ 1 had better top-quality embryo rates.
Conclusion: The study identified the hLH/bLH ratio as a potential predictor of the impact of LH levels on embryo development potential and pregnancy outcomes in women with PCOS undergoing GnRH-antagonist stimulation cycles.

Keywords: Polycystic ovary syndrome, flexible GnRH antagonist, luteinizing hormone, *in vitro* fertilization, intracytoplasmic sperm injection

Introduction
Polycystic Ovary Syndrome (PCOS) is a prevalent endocrine disorder affecting 5-10% of women of reproductive age [1]. It has a higher prevalence in Mexican-Americans compared to non-Hispanic whites and African Americans [2]. PCOS is characterized by persistent anovulation, hyperandrogenemia, and polycystic ovarian morphology, often associated with insulin resistance. It is linked to various morbidities, including endometrial cancer, depression, obstructive sleep apnea, obesity, metabolic syndrome, type 2 diabetes mellitus (T2DM), and cardiovascular risks [3].

Luteinizing hormone (LH) and follicle-stimulating hormone (FSH), secreted by the anterior pituitary, are indicators of ovarian reserve, with the LH/FSH ratio predicting ovarian responsiveness. LH plays a crucial role in follicular development and ovum maturation. Women with PCOS exhibit elevated LH and reduced FSH levels, leading to a higher LH/FSH ratio, increased androgen synthesis, and hyper-recruitment of oocytes [4]. Insulin resistance and hyperinsulinemia drive hyperandrogenemia in most PCOS patients [5]. Additionally, about 25% of PCOS patients have elevated prolactin levels [6]. Chronic inflammation and increased oxidative stress are associated with PCOS, and antioxidants have been shown to improve several clinical and metabolic parameters in these patients [7]. Infertility, defined by the WHO as the inability to conceive after 12 months of unprotected intercourse, affects 10% of the global population, with the highest rates in the Middle East, North Africa, and Eastern Europe [8, 9]. Pregnancy rates in PCOS patients are lower due to excessive LH secretion and premature LH surges, leading to poor oocyte quality, early meiosis, and reduced implantation rates [10,11]. Adverse pregnancy outcomes in PCOS patients may stem from hyperandrogenemia, hyperinsulinemia, and abnormal follicular and uterine environments [12, 13]. Ovulatory disorders account for 25% of female infertility cases, alongside tubal and uterine factors such as endometriosis, fibroids, and scarring [14, 15].

Management strategies for PCOS-related infertility include lifestyle modifications, pharmacotherapy, surgical interventions, and assisted reproductive technology (ART) [16]. ICSI is the preferred method to maximize fertilization and reduce polyspermy, with the GnRH antagonist protocol being a safer option to minimize gonadotropin dosage and OHSS incidence [17, 18]. PCOS patients often exhibit increased serum LH and an elevated LH/FSH ratio, impairing follicular maturation and fertility [19, 20]. Early LH peaks during antagonist protocols may affect oocyte and embryo quality, but findings remain inconsistent due to population differences [21, 22]. This study aims to evaluate serum LH levels at various time points during COS cycles and their impact on IVF/ICSI outcomes, including oocyte retrieval, top-quality embryos, pregnancy rates, and live birth rates.

Methods

This prospective cohort study was conducted at the Center for Infertility in Kamal Al-Samarri Teaching Hospital, Baghdad, over a 10-month period (January to October 2024). The study included 90 infertile women with PCOS, aged 18-40 years and with BMI between 18.5 and <30 kg/m², undergoing a GnRH-antagonist stimulation protocol with fresh cycle embryo transfer. Participants were divided into three groups based on basal LH (bLH), LH on HCG trigger day (hLH), and the hLH/bLH ratio.

Grouping Strategies

- bLH (mIU/mL): ≤5, 5-10, ≥10
- hLH (mIU/mL): ≤2, 2-5, ≥5
- hLH/bLH Ratio: ≤0.5, 0.5-1.0, ≥1

bLH (mIU/mL)			hLH (mIU/mL)			hLH/bLH Ratio		
Group 1	Group 2	Group 3	Group 1	Group 2	Group 3	Group 1	Group 2	Group 3
≤5	5-10	≥10	≤2	2-5	≥5	≤0.5	0.5-1.0	≥1

bLH: based on basal LH, hLH: LH level on trigger day.

Patient Selection: Patients with primary infertility and PCOS were recruited from infertility centers. Inclusion criteria included PCOS diagnosis, BMI 18.5-<30 kg/m², and fresh cycle embryo transfer. Exclusion criteria included male factor infertility, tubal factor infertility, endometriosis, prior ICSI cycles, and frozen embryo transfers. Baseline assessments included questionnaires on demographics, infertility history, hormonal profiles (FSH, LH, AMH, E2, prolactin), and ultrasound on day 2 of the cycle.

Ovarian Stimulation Protocol: Patients underwent ovarian stimulation with recombinant FSH (rFSH) or combined rFSH and hMG. Dosages were adjusted based on ovarian response, monitored via serum estrogen and ultrasound. GnRH antagonist (Cetrorelix) was introduced when follicles reached 12-14 mm. Final oocyte maturation was triggered with HCG when follicles reached ≥18 mm, followed by transvaginal ovum pickup 34-36 hours later.

Embryo Transfer and Luteal Support: Fertilization was achieved via IVF or ICSI based on sperm quality. Embryos were graded and transferred under transabdominal ultrasound guidance. Luteal phase support included intramuscular progesterone and oral Duphaston. Progesterone was maintained until 8-10 weeks of gestation in cases of pregnancy.

Outcome Measures: Primary outcomes included the number of oocytes retrieved, cumulative chemical pregnancy rate, clinical pregnancy rate, and live birth rate. Secondary outcomes included 2PN count, top-quality embryo ratio, and total gonadotropin dosage. Chemical pregnancy was defined as serum β-HCG >10 IU/L, while clinical pregnancy required ultrasonographic detection of a gestational sac with fetal heart activity.

Statistical Analysis: Data were analyzed using SPSS 22.0. Comparisons of means used t-tests or Mann-Whitney tests, and categorical variables were compared using χ2-tests. Statistical significance was defined as $p< 0.05$.

Results

A total of 90 infertile PCOS women were included in this study. All of them were undergoing GnRH-antagonist stimulation protocol. The baseline information and ICSI outcomes were studied and compared using different grouping strategies. There were no statistically significant differences in age, BMI, and AMH level among various groups in all three strategies. In this study, women were divided according to LH level at basal, at the day of trigger, and the ratio of LH level on HCG trigger day to basal LH level.

Patients were divided into three groups:

Group 1: LH level < 5 m IU/ml.
Group 2: LH level 5 - 10 m IU/ml.
Group 3: LH level > 10 m IU/ml.

We noticed no evidence of significant differences in all baseline characteristics, hormones, and ICSI outcomes according to basal LH levels ($p\geq 0.05$). As illustrated in (Table 1).

Table 1: Comparison of baseline characteristics, hormonal parameters, and ICSI outcomes according to basal LH level.

Variable	Basal serum LH (m IU/mL)			P- value
	< 5 (n= 40)	5 - 10 (n= 29)	> 10 (n= 21)	
Age (Years)	25.64 ± 4.05	26.73 ± 3.69	25.33 ± 4.11	0.736
BMI (Kg/m^2)	24.52 ± 2.18	25.66 ± 3.45	26.11 ± 3.09	0.178
AMH (ng/ml)	2.08 ± 1.54	1.94 ± 1.32	2.15 ± 1.73	0.522
Basal LH (mIU/mL)	3.06 ± 1.02	5.92 ± 1.15	9.83 ± 3.14	0.431
Basal FSH (IU/L)	7.12 ± 1.84	7.02 ± 2.61	6.97 ± 1.73	0.814
Estradiol (pg/ml)	1491.3 ± 531	1361.1 ± 629	1574.2 ± 529	0.109
Prolactin (ng/ml)	14.61 ± 4.27	14.15 ± 5.16	13.21 ± 4.10	0.321
Progesterone (ng/ml)	1.74 ± 1.19	1.71 ± 1.21	1.69 ± 1.19	0.817
Total Gn. Dose	2187 ± 555	2101 ± 491	2196 ± 561	0.412
No. of growing follicles	6.45 ± 2.25	5.67 ± 2.89	6.07 ± 2.89	0.745
No. of oocytes retrieved	8.89 ± 2.52	6.56 ± 2.67	5.94 ± 2.04	0.094
No. of fertilized oocytes	3.11 ± 1.15	2.38 ± 1.03	3.74 ± 1.08	0.183
Total No. of embryos	5.9 ± 3.4	4.31 ± 3.5	5.21 ± 4.10	0.621
Transferred embryo	1.89 ± 0.92	1.65 ± 0.73	1.67 ± 0.97	0.679
Embryo grade I	2.73 ± 0.94	2.79 ± 1.02	2.82 ± 0.87	0.916
Embryo grade II	1.69 ± 0.81	2.65 ± 1.91	2.65 ± 0.93	0.668

Embryo grade III	3.50 ± 0.93	2.72 ± 1.05	2.21 ± 0.89	0.413
Top quality embryo%	39.10	37.12	38.35	0.068
Biochemical pregnancy%	73.41	78.53	71.68	0.118
Clinical pregnancy%	33.21	34.46	34.22	0.514
Live birth%	28.90	31.72	26.11	0.319

After controlled ovarian stimulation, the flexible protocol of recombinant follicle-stimulating hormone (rFSH) alone or combined with hMG was used. The gonadotropin dose was adjusted according to ovarian responses assessed by serum estrogen levels and ultrasonography. Ultrasound examination and serum FSH, LH, E2, and P measurements were performed after 4-5 days of controlled ovarian hyperstimulation.

LH level on HCG trigger day

Patients were divided into three groups:

Group 1: LH level < 2 m IU/ml.

Group 2: LH level 2 - 5 m IU/ml.

Group 3: LH level > 5 m IU/ml.

The comparison of baseline characteristics, hormonal parameters, and ICSI outcomes according to LH levels on the trigger day showed a significant difference in basal FH and LH levels, and chemical & clinical pregnancy rates. Patients in group 1 had significantly lower FH and LH levels compared to patients in groups 2 and 3 (6.97 m IU/ml vs. 8.95 m IU/ml and 9.02 m IU/ml, P= 0.001; and 4.53 m IU/ml vs. 7.22 m IU/ml and 7.94 m IU/ml, P= 0.001) respectively. Further, patients in group 1 had a significantly higher chemical pregnancy rate (79.03 vs. 67.53 and 69.14, P= 0.001) and clinical pregnancy rate (36.18 vs. 28.53 and 29.71, P= 0.001). Other variables showed no significant difference regarding LH levels on trigger day (P ≥ 0.05). As illustrated in (Table 2).

Table 2: Comparison of baseline characteristics, hormonal parameters, and ICSI outcomes according to LH level on trigger day.

Variable	LH level on trigger day (m IU/mL)			P- value
	< 2 (n= 47)	2 - 5 (n= 18)	> 5 (n= 25)	
Age (Years)	27.04 ± 4.22	26.11 ± 3.12	26.72 ± 4.36	0.834
BMI (Kg/m^2)	25.31 ± 3.07	26.14 ± 3.95	27.02 ± 3.10	0.098
AMH (ng/ml)	2.08 ± 1.54	1.94 ± 1.32	2.15 ± 1.73	0.522
Estradiol (p g/ml)	1352.4 ± 604	1398.3 ± 594	1443.1 ± 622	0.110
LH (m IU/mL)	4.53 ± 2.48	7.22 ± 2.41	7.94 ± 2.36	0.001
FSH (m IU/mL)	6.97 ± 1.86	8.95 ± 1.77	9.02 ± 2.61	0.001
Prolactin (ng/ml)	13.11 ± 3.98	14.23 ± 4.26	14.14 ± 4.92	0.526
Progesterone (ng/ml)	1.89 ± 0.97	2.02 ± 1.01	1.71 ± 0.91	0.913
Total Gn. Dose	2019 ± 532	2103 ± 544	2101 ± 551	0.412
No. of growing follicles	7.14 ± 2.81	5.02 ± 2.33	6.16 ± 2.38	0.097
No. of oocytes retrieved	9.29 ± 2.34	10.44 ± 2.18	10.23 ± 2.56	0.224
No. of fertilized oocytes	3.35 ± 1.09	3.02 ± 1.11	3.24 ± 1.73	0.986
Total No. of embryos	6.34 ± 3.06	6.73 ± 3.10	5.87 ± 3.10	0.734
Transferred embryo	1.75 ± 0.81	1.82 ± 0.67	1.89 ± 0.93	0.774
Embryo grade I	2.83 ± 0.67	2.90 ± 0.92	2.57 ± 0.90	0.892
Embryo grade II	2.94 ± 0.78	2.16 ± 1.12	2.34 ± 1.05	0.523
Embryo grade III	2.56 ± 1.02	2.91 ± 1.10	3.85 ± 1.04	0.094
Top quality embryo%	36.24	35.34	37.22	0.128
Biochemical pregnancy%	79.03	67.53	69.14	0.012
Clinical pregnancy%	36.18	28.53	29.71	0.024
Live birth	24.35	26.29	34.68	0.059

Ratio of LH on trigger day to basal LH level

Patients were divided into three groups:

Group 1: LH level < 0.5 m IU/ml.

Group 2: Those with LH level 0.5 - 1 m IU/ml.

Group 3: Those with LH level > 1 m IU/ml.

By comparison of baseline characteristics, hormonal parameters, and ICSI outcomes according to the ratio of LH on trigger day to basal LH level, we found that patients in group 3 consumed significantly higher gonadotropin dosages than those in groups 1 and 2 (2438.5 IU vs 1918.3 IU and 1904.2 IU, P= 0.009) respectively. The top-quality embryo rate was significantly higher in group 3 than the other two groups (39.36 vs 34.19 and 32.50, P= 0.001). On the other hand, the chemical and clinical pregnancy rates were significantly higher among patients in group 1 than those in the other two groups (77.43 vs. 64.35 and 67.22, P= 0.001) and (38.84 vs. 33.12 and 31.23, P= 0.001). Other variables were not significantly different between the three groups of this ratio ($p \geq 0.05$). As illustrated in (Table 3).

Table 3: Comparison of baseline characteristics, hormonal parameters, and ICSI outcomes according to the ratio of LH on trigger day to basal LH level

Variable	LH on trigger day/Basal LH ratio			P- value
	< 0.5 (n= 53)	0.5 -1 (n= 20)	> 1 (n= 17)	
Age (Years)	26.34 ± 4.15	25.25 ± 4.51	26.13 ± 4.40	0.875
BMI (Kg/m^2)	26.20 ± 3.43	26.06 ± 4.05	24.38 ± 3.74	0.117
AMH (ng/ml)	1.96 ± 0.82	2.22 ± 1.17	2.07 ± 1.01	0.176
Estradiol (p g/ml)	1453.2 ± 542	1420.1 ± 581	1396.2 ± 578	0.318
FSH (m IU/mL)	7.44 ± 2.31	7.15 ± 1.23	8.36 ± 2.54	0.097
LH (m IU/mL)	7.22 ± 2.17	6.13 ± 2.95	6.34 ± 2.16	0.235
Prolactin (ng/ml)	14.41 ± 3.26	13.98 ± 3.67	14.01 ± 4.05	0.483
Progesterone (ng/ml)	2.12 ± 1.02	1.94 ± 0.95	1.84 ± 0.78	0.716
Total Gn. Dose	1918.3 ± 568	1904.2 ± 552	2438 ± 583	0.009
No. of growing follicles	7.06 ± 2.32	6.34 ± 2.11	7.17 ± 2.53	0.281
No. of oocytes retrieved	10.43 ± 2.37	9.89 ± 3.03	11.02 ± 2.78	0.127
No. of fertilized oocytes	3.54 ± 1.13	3.60 ± 1.46	2.98 ± 1.08	0.492
Total No of embryos	6.65 ± 2.56	5.89 ± 2.01	5.77 ± 2.10	0.734
Transferred embryo	1.91 ± 0.72	1.73 ± 0.80	1.82 ± 0.81	0.223
Embryo grade I	2.55 ± 0.57	2.81 ± 0.63	2.78 ± 0.53	0.520
Embryo grade II	2.43 ± 0.65	2.36 ± 0.88	2.60 ± 1.01	0.201
Embryo grade III	2.47 ± 0.98	3.54 ± 0.72	2.61 ± 1.04	0.113
Top quality embryo%	34.19	32.50	39.36	0.001
Biochemical pregnancy%	77.43	64.35	67.22	0.001
Clinical pregnancy%	38.84	33.12	31.23	0.001
Live birth	22.74	25.89	33.62	0.072

Discussion

In recent years, GnRH-antagonist protocols have become the preferred approach for controlled ovarian hyperstimulation (COH) in women with PCOS due to their ability to reduce the risk of ovarian hyperstimulation syndrome (OHSS). A critical aspect of COH is the suppression of premature LH surges by GnRH antagonists, though these protocols do not entirely prevent early LH peaks. Elevated LH levels during stimulation, particularly in women with high basal LH (bLH), can lead to premature ovulation, reduced oocyte quality, and impaired endometrial receptivity, raising concerns about the impact of LH levels on IVF/ICSI outcomes. Several studies have explored the relationship between LH levels and reproductive outcomes in PCOS. Bin Wang *et al*. (2023) demonstrated that basal LH >11.7 IU/mL was associated with a higher miscarriage rate in PCOS women undergoing COH with IUI [23]. While our study included 90 PCOS women with bLH >10 in only 21 cases, we observed no significant effect of bLH on clinical outcomes such as biochemical pregnancy, clinical pregnancy, or live birth rates. In contrast, we found that women with hLH ≤2 mIU/mL on the trigger day had improved pregnancy outcomes, including biochemical and clinical pregnancy rates. The hLH/bLH ratio has also been suggested as a useful index for evaluating LH dynamics during stimulation. In our study, the hLH/bLH ratio <0.5 group had the highest pregnancy rates despite lower rates of top-quality embryos compared to the ≥1.0 group. This discrepancy indicates that embryo grading may not fully reflect developmental potential and suggests the influence of endometrial receptivity and other factors. Additionally, patients in the ≥1.0 group had higher gonadotropin consumption, likely related to higher BMI, which is associated with elevated LH levels and reproductive dysfunction in PCOS women [24]. Findings from other studies further support the importance of hLH levels. Ruiqiong Zhou *et al*. (2023) reported that higher LH levels on the trigger day were associated with improved live birth rates (LBR) in PCOS women undergoing GnRH-antagonist protocols, likely due to enhanced implantation rates [25]. Conversely, Qianjie Zhang found that LH levels ≥3.14 IU/L on the trigger day predicted poor pregnancy outcomes in diminished ovarian reserve (DOR) patients [26]. Similarly, Conghui Pang *et al*. (2021) observed better implantation rates in PCOS patients with hLH levels of 5-10 IU/L compared to <1 IU/L, suggesting that moderate LH levels during stimulation may optimize outcomes [27]. High LH levels in PCOS women are linked to premature luteinization, poor oocyte quality, and reduced endometrial receptivity, particularly in cases with elevated basal LH or obesity [28]. Increasing the GnRH antagonist dose can mitigate these effects by reducing LH to normal levels. However, a unified standard for defining early LH peaks is lacking, with most studies considering LH ≥10 IU/L as a threshold [22]. Our findings highlight the significance of the hLH/bLH ratio as a dynamic marker of LH changes during stimulation, which may influence embryonic development and pregnancy outcomes. Further research is needed to establish optimal LH thresholds for tailored management of PCOS patients undergoing IVF/ICSI.

Conclusion

Our research demonstrated that variations in serum LH levels within the GnRH-antagonist protocol may adversely affect pregnancy outcomes in women with polycystic ovary syndrome (PCOS) undergoing IVF/ICSI treatment. Furthermore, the ratio of hLH to bLH may serve as a more sensitive metric for assessing LH levels in relation to the potential for embryo development in women with PCOS within a GnRH-antagonist framework. Nonetheless, owing to the retrospective design of this study, particularly the limited number of cases involving frozen embryo transfer, there exists the potential for selection bias, and consequently, the clinical conclusions drawn may be subject to certain limitations. Future research endeavours will expand the cohort of women diagnosed with polycystic ovary syndrome (PCOS) to facilitate a more comprehensive examination of the influence of luteinizing hormone (LH) levels on *in vitro* fertilisation (IVF) and intracytoplasmic sperm injection (ICSI) outcomes, with particular emphasis on the cumulative live birth rate. This will enhance the understanding of its influence on the outcomes of IVF/ICSI; however, additional research is required to substantiate this conclusion.

Conflict of Interest
Not available

Financial Support
Not available

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