ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

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Low Serum LH Levels on hCG Trigger Day are Associated with Reduced Live Birth Rates in GnRH Antagonist Cycles

GnRH Antagonisti Sikluslarında hCG Tetikleme Gününde Düşük Serum LH Düzeyleri Canlı Doğum Oranlarının Azalmasıyla İlişkilidir

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ABSTRACT

Objective: To investigate the association between LH levels on hCG trigger day and reproductive outcomes in patients undergoing GnRH antagonist stimulation followed by fresh embryo transfer. **Materials and Methods:** A retrospective cross-sectional study was conducted at a university-based infertility clinic between January 2015 and December 2022. The study included normoresponder women aged 40 or younger who underwent fresh, non-donor intracytoplasmic sperm injection (ICSI) or in vitro fertilization (IVF) treatment cycles using a GnRH antagonist protocol. **Results:** 105 patients were included in this study. Among them, 41 patients achieved live births. Significant differences in age and serum LH levels on the hCG trigger day were observed between patients who achieved live birth and those who did not, but no significant differences in terms of progesterone levels on trigger day, number of oocytes retrieved, embryo quality, or number of mature (MII) oocytes. The ROC analysis identified an LH threshold of 2.7 mUI/ml with optimal sensitivity and specificity. Older women are at higher risk of unsuccessful pregnancy outcomes (Pregnancy: RR=1.1, 95% CI=1.014-1.194, p=0.022; Live Birth: RR=1.082, 95% CI=0.997-1.174, p=0.06). Age-adjusted multivariate regression analysis revealed a 4.7-fold decrease in pregnancy rates (95% CI=1.929-11.44, p=0.001) and 4.1-fold (95% CI=1.730-9.706, p=0.001) in live birth rates among patients with lower LH levels (≤2.7 mUI/ml). **Conclusion:** An LH threshold of 2.7 mIU/ml on the hCG trigger day can be used to predict unsuccessful pregnancy outcomes. A freeze-all strategy might be a prudent choice for the normoresponder women with low LH levels on trigger day.

Keywords: Luteinizing hormone, hCG trigger, GnRH antagonist, fresh embryo transfer, live birth

ÖZET

Amaç: GnRH antagonisti stimülasyonu ve taze embriyo transferi uygulanan hastalarda hCG trigger gününde LH seviyeleri ile üreme sonuçları arasındaki ilişkiyi araştırmak. **Gereç ve Yöntemler:** Ocak 2015 ile Aralık 2022 arasında üniversite merkezli bir infertilite kliniğinde retrospektif kesitsel bir çalışma yürütüldü. Çalışmaya, GnRH antagonisti protokolü kullanılarak taze, donör olmayan intrasitoplazmik sperm enjeksiyonu (ICSI) veya in vitro fertilizasyon (IVF) tedavi döngüleri uygulanan 40 yaş ve altı normoresponder kadınlar dahil edildi. **Bulgular:** Bu çalışmaya 105 hasta dahil edildi. Bunlardan 41'i canlı doğum yaptı. Canlı doğum yapan ve yapmayan hastalar arasında hCG trigger gününde yaş ve serum LH seviyeleri açısından anlamlı farklılıklar gözlendi, ancak trigger gününde progesteron seviyeleri, alınan oosit sayısı, embriyo kalitesi veya olgun (MII) oosit sayısı açısından anlamlı bir fark görülmedi. ROC analizi, optimum duyarlılık ve özgüllük ile 2,7 mUI/ml'lik bir LH eşiği belirledi. İleri kadın yaşı, gebelik başarısızlık oranını anlamlı ölçüde artıran bir risk faktörü olarak görüldü (Gebelik: RR=1,1, %95 CI=1,014-1,194, p=0,022; Canlı Doğum: RR=1,082, %95 CI=0,997-1,174, p=0,06). Yaşa göre ayarlanmış çok değişkenli regresyon analizi, düşük LH seviyelerine sahip hastalarda (≤2,7 mUI/ml) gebelik oranlarında 4,7 kat (95% CI=1,929-11,44, p=0,001) ve canlı doğum oranlarında 4,1 kat (95% CI=1,730-9,706, p=0,001) düşüş olduğunu ortaya koydu. **Sonuç:** hCG trigger gününde 2,7 mIU/ml'lik bir LH eşiği, başarısız gebelik sonuçlarını tahmin etmek için kullanılabilir. Trigger gününde düşük LH seviyelerine sahip normoresponder kadınlar için bir freeze-all stratejisi ihtiyatlı bir tercih olabilir.

Anahtar Kelimeler: Luteinize edici hormon, hCG trigger, GnRH antagonisti, taze embriyo transferi, canlı doğum

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The gonadotropin-releasing hormone (GnRH) antagonist protocol has become a widely adopted approach for controlled ovarian stimulation (COS) due to its convenience, safety, and comparable efficacy to the traditional GnRH agonist long protocol.[1] GnRH antagonists rapidly and reversibly bind to pituitary GnRH receptors. The timing and dosage of GnRH antagonists in in-vitro fertilization (IVF)/ intracytoplasmic sperm injection (ICSI) cycles can influence endogenous luteinizing hormone (LH) levels.[2,3] LH levels and the effects on outcomes of GnRH antagonist stimulation cycles can differ significantly among individuals.[4,5]

LH plays a critical role in various reproductive processes, including follicular development, oocyte maturation, steroidogenesis, embryo implantation, and corpus luteum function.[6-8] Fluctuations in LH levels during the follicular phase significantly influence the oocyte's morphological and functional characteristics, impacting its meiotic state and fertilization potential.[9] Despite its importance, the optimal LH range during the follicular phase for COS remains unclear. The association between LH concentrations and pregnancy outcomes in GnRH antagonist cycles remains debatable, with limited research available. Some studies have found no association between LH levels and clinical outcomes, while others have linked low LH levels to adverse pregnancy outcomes.[4,10-14] Existing studies exhibit heterogeneity in stimulation protocols, patient characteristics, LH measurement timing, and LH cut-off values.

The primary objective of this study was to investigate the association between LH levels on hCG trigger day and reproductive outcomes in patients undergoing GnRH antagonist stimulation followed by fresh embryo transfer. A secondary objective was to identify an optimal pre-trigger serum LH threshold, if applicable.

MATERIALS AND METHODS

A retrospective cross-sectional study was conducted at a university-based infertility clinic between January 2015 and December 2022. Participants were women aged 40 or younger undergoing fresh, non-donor ICSI or IVF treatment following a GnRH antagonist protocol. Patient data and follow-up information were extracted from medical records. This study was conducted following the principles of the Declaration of Helsinki 2008. The institutional Ethics Committee approved the study protocol (No: I08-626-24, Date: 30.09.2024). The inclusion criteria of cases were as follows: (1) ICSI or IVF treatment following a GnRH antagonist protocol; (2) women ≤ 40 years at the time of IVF cycle; (3) patients followed up until the end of IVF treatment or first live birth or cycles that ended in a miscarriage or stillborn. Exclusion criteria were as follows: (1) women without follow-up information; (2) freezing of all retrieved oocytes/embryos; (3) women with abnormal basal FSH, TSH, and prolactin levels; (4) women with PCOS according to Rotterdam criteria, poor responder status according to POSEIDON criteria, recurrent abortions, and uterine abnormalities.[15,16]

Ovarian stimulation began on days 3-4 of the menstrual cycle. The starting dosage was tailored individually, including age, ovarian reserve, and BMI. Subsequent adjustments were made based on ovarian response. All patients received antagonist protocol (Cetrotide; Merck-Serono, Istanbul, Turkey) after five days of gonadotropin use or when at least one 12-mm follicle was observed. Gonadotropin stimulation was initiated with either hMG menotropin (Menogon, Ferring, Kiel, Germany; or Menopur, Ferring, Kiel, Germany) or recombinant FSH (Gonal-F; Merck-Serono, Geneva, Switzerland), or a combination of both.

As a routine clinical procedure in our center, blood samples were collected on the second or third day of the menstrual cycle, 4-5 days after initiating gonadotropin stimulation, and then every 1-2 days until the hCG trigger day.

Ovulation was triggered with human chorionic gonadotropin (hCG) in all cycles. Luteal phase support consisted of vaginal progesterone at 90 mg/day (Crinone 8% gel; Merck-Serono) from embryo transfer to 12 weeks of gestation. Antenatal follow-ups adhered to the guidelines of the Turkish Ministry of Health.

Demographic data included age, infertility indication, and ovarian reserve assessment on day 3 of

the menstrual cycle. Cycle characteristics encompassed total gonadotropin dose, cycle duration, ovarian induction drugs, and sonographic assessments of follicles and endometrium. Transfer characteristics included endometrial thickness, embryo quality (using established scoring systems, and embryo age. The primary outcome measure was live birth, defined as the delivery of a live-born neonate.[17,18] A positive quantitative serum hCG test determined pregnancy.

Patients were divided into two groups based on live birth (LB). Both groups were compared regarding age, AFC, AMH, FSH, LH, progesterone, estradiol levels, duration of stimulation, gonadotropin dosage, and oocyte and embryo quality and quantity.

STATISTICAL ANALYSIS

Data analysis was performed using SPSS version 21.0 (IBM Corporation, Armonk, NY, USA). Shapiro-Wilk tests were conducted to assess the normality of distributions. Mann-Whitney U-tests or t-tests were used accordingly. For categorical variables, Chi-square tests or Fisher's exact tests were employed. A receiver operating characteristic (ROC) analysis was conducted to determine an optimal LH threshold. Reproductive outcomes were then compared based on this threshold. Univariate and multivariate logistic regression analyses were performed to evaluate the influence of LH levels on clinical outcomes, controlling for potential confounders. A p-value <0.05 was considered statistically significant.

RESULTS

105 patients meeting the inclusion and exclusion criteria were included in this study. Among them, 41 patients achieved live births. A comparison of baseline characteristics was conducted between patients who achieved live birth and those who did not (Table 1). Age and serum LH levels on the hCG trigger day differed significantly between the two groups. There were no significant differences between the two groups in terms of progesterone levels on trigger day (Live birth: 1.06 [0.87-1.4]; No live birth: 1 [0.68-1.57]; p=0.58), number of oocytes retrieved (Live birth: 9 [6-13.5]; No live birth: 8 [5-11.75]; p=0.7), embryo quality (Live birth: 1 [1-3]; No live birth: 1 [0-2]; p=0.07), or number of mature (MII) oocytes (Live birth: 9 [5-10]; No live birth: 6 [3.5-9.5]; p=0.09). While the live birth group exhibited a slightly higher number of mature (MII) oocytes and better embryo quality than the no-live birth group, this difference did not reach statistical significance.

TABLE 1: Comparison of baseline characteristics according to whether patients achieved a live birth after fresh embryo transfer.

	Live Birth (n=41)	No live birth (n=64)	p
Age (Years)	30 [25-35.5]	32 [28-37]	0.03[2]
AMH (ng/ml)	1.8 [0.75-3.53]	1.4 [0.8-3.28]	0.95[2]
AFC	10.46±3.17	9.86±4.22	0.41[1]
FSH on D3 (mUI/ml)	6.7 [5-8.1]	6.9 [6-8]	0.55[2]
Estradiol on D3 (pg/ml)	46 [31-63.4]	44 [35.3-68.0]	0.86[2]
LH on D3 (mUI/ml)	4 [2.55-5.55]	4.7 [3-6]	0.55[2]
Endometrial thickness on trigger day	10.51±2.77	10.14±2.05	0.47[1]
Total FSH/hMG (IU)	2400 [1800-2887.5]	2250 [1913.25-2681.25]	0.5[2]
Starting day of antagonist administration	8 [7-9]	7 [7-8]	0.32[2]
Total days of stimulation	9 [8-10]	9.5 [8-11]	0.64[2]
Progesterone on trigger day (nmol/L)	1.06 [0.87-1.4]	1 [0.68-1.57]	0.58[2]
Estradiol on trigger day (pg/ml)	1885 [1169-3194]	1409 [872.5-3036.75]	0.87[2]
LH on trigger day (mUI/ml)	2.9 [1.48-4]	1.78 [1-2.7]	0.01[2]
Follicles ≥14 mm on trigger day	7 [5-9]	6 [4-8]	0.15[2]
Follicles ≥17 mm on trigger day	4 [2-4]	3 [2-5]	0.73[2]
No. of oocytes retrieved	9 [6-13.5]	8 [5-11.75]	0.7[2]
No. of MII oocytes	9 [5-10]	6 [3.5-9.5]	0.09[2]
No. of embryos	3 [1-5]	2 [1.25-5]	0.54[2]
QTE	1 [1-3]	1 [0-2]	0.07[2]

Abbreviations: AMH: Anti-Müllerian hormone; AFC: Antral follicle count; FSH: Follicle stimulating hormone; D3: Day 3; LH: Luteinizing hormone; MII: Metaphase II oocyte; TQE: Top quality embryo; hMG: Human menopausal gonadotropin
[1]T-test; Mean ± SD;
[2]Mann-Whitney-U-Test; Median [Q25-75]

The ROC analysis identified an LH threshold of 2.7 mUI/ml with optimal sensitivity and specificity. Figure 1 and Figure 2 present box plots illustrating the distribution of LH levels on the trigger day regarding pregnancy and live birth rates. When stratifying patients by this threshold, significant differences in pregnancy rates and live birth rates were observed (Table 2). A significant decrease in pregnancy and live birth rates was observed in patients with lower LH levels on trigger day (≤2.7 mUI/ml) (Table 2).

To investigate the relationship between LH levels on trigger day and pregnancy and live birth rates

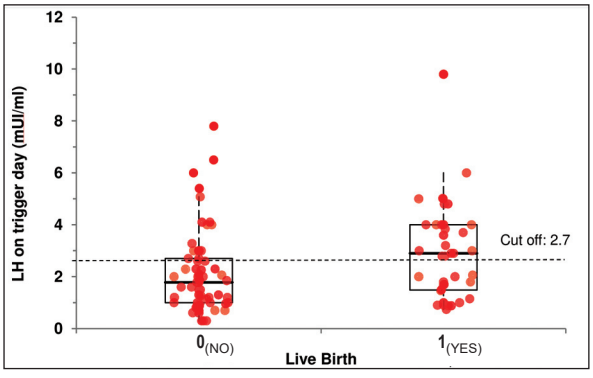

FIGURE 1: Relationship between LH on trigger day and live birth.

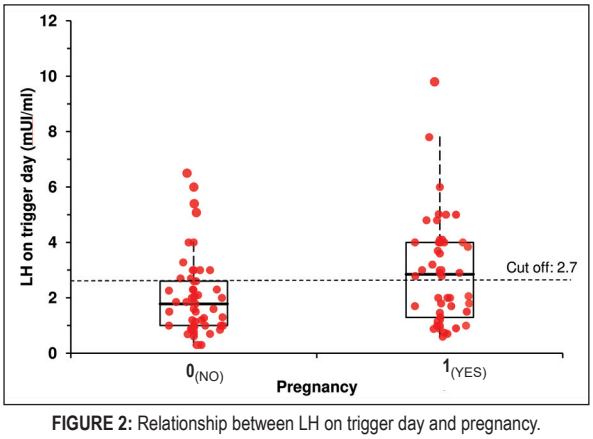

FIGURE 2: Relationship between LH on trigger day and pregnancy.

TABLE 2: Pregnancy outcomes following fresh embryo transfer with an LH threshold of 2.7 mIU/ml on the hCG trigger day.

	Group 1 (LH on trigger day ≤2.7 mUI/ml) (n=67)	Group 2 (LH on trigger day >2.7 mUI/ml) (n=38)	p
Pregnancy rate	23 (34.33%)	27 (71.05%)	<0.001
Miscarriage rate	5 (7.46%)	4 (10.53%)	0.53
Live Birth rate	18 (26.87%)	23 (60.53%)	0.001

univariable and multivariable regression analyses were conducted. Older women are at higher risk of unsuccessful pregnancy outcomes (Pregnancy: RR=1.1, 95% CI=1.014-1.194, p=0.022; Live Birth: RR=1.082, 95% CI=0.997-1.174, p=0.06). Age-adjusted multivariate regression analysis revealed a 4.7-fold decrease in pregnancy rates (95% CI=1.929-11.44, p=0.001) and 4.1-fold (95% CI=1.730-9.706, p=0.001) in live birth rates among patients with lower LH levels (≤2.7 mUI/ml) (Table 3A and 3B).

TABLE 3A: Multivariable regression analysis for live birth after fresh embryo transfer

	p	Adjusted RR (95% CI)
Age	0.060	1.082 (0.997-1.174)
LH on trigger day ≤2.7	0.001	4.098 (1.730-9.706)

TABLE 3B: Multivariable regression analysis for pregnancy after fresh embryo transfer

	p	Adjusted RR (95% CI)
Age	0.022	1.1 (1.014-1.194)
LH on trigger day ≤2.7	0.001	4.698 (1.929-11.44)

DISCUSSION

The present study showed that lower LH levels on the hCG trigger day were associated with reduced pregnancy and live birth rates in normogonadotropic patients undergoing GnRH antagonist cycles with fresh embryo transfer. Age-adjusted multivariate regression analysis revealed a 4.7-fold decrease in pregnancy rates and 4.1-fold in live birth rates among patients with lower LH levels (cut-off: ≤2.7 mUI/ml).

Luo et al. demonstrated a significant reduction in LBR among patients with low LH levels (38.0% vs. 51.5%) following fresh embryo transfer (14). Their study included 1480 normogonadotropic women undergoing COH with GnRH Antagonist Protocol. However, their arbitrary LH cutoff of 4 IU/L may not be the most appropriate for patient stratification. The mean LH levels on the trigger day of the lower LH group was 2.11 ± 1.01(IU/L); in the high LH group, it was 3.13 ± 1.92 (IU/L). This finding further supports the validity of our established LH threshold of 2.7 mIU/ml, effectively differentiating between groups with favorable and unfavorable pregnancy outcomes.

Chen et al. suggested an LH cut-off to the entire cycle of 0.8 mIU/ml that was established as the optimal cutoff for predicting early pregnancy loss based on logistic regression analysis of the study data.[13] Since our focus was LBR, these results are also consistent with our study. Furthermore, Benmachiche et al. found that low serum LH levels on the day of the

GnRH-agonist trigger are associated with decreased live birth rates and increased early miscarriage rates.[19] The inconsistent findings in the literature may be attributed to variations in the definition of low LH, LH measurement parameters, and clinical interventions.

Our findings suggest that lower LH levels on the trigger day significantly decrease the likelihood of live birth rates after fresh embryo transfer, even when cycle duration, progesterone levels on trigger day, average number of oocytes retrieved, MII oocytes, and embryo quality and quantity were comparable. These findings highlight the importance of LH levels in optimizing reproductive outcomes. The exact mechanism by which low pre-trigger LH levels contribute to reduced pregnancy rates is not fully understood. Low serum LH levels might contribute to asynchrony between the embryo and the endometrium, potentially leading to implantation failure and poor reproductive outcomes. Luteinizing hormone (LH) exerts its biological effects primarily through binding to the LH receptor (LHCG-R), which is predominantly expressed in ovarian theca, mural granulosa, and luteal cells.[20] Notably, LHCG-Rs are also detected in oocytes, preimplantation embryos, and the endometrium, suggesting LH's direct influence on oocyte quality, embryo growth, implantation, and corpus luteum function.[21,22] Bildik et al. highlighted that luteal granulosa cells in stimulated IVF cycles exhibit reduced viability, decreased expression of LH receptors and anti-apoptotic genes, and impaired hormone production compared to natural cycles.[23] While these findings suggest a potential link between low LH levels and impaired endometrial function, the precise impact of low LH on oocyte/embryo quality and corpus luteum function during controlled ovarian stimulation remains unclear. Further research is necessary to elucidate these associations.

Despite significant differences in LH levels on trigger day, progesterone levels remained comparable between the live birth and no live birth groups. Importantly, neither group showed signs of premature luteinization, as evidenced by the absence of excessive increases in progesterone levels on the trigger day. Previous studies have suggested that premature LH increases, indicative of premature luteinization, may negatively impact oocyte yield and embryo implantation due to elevated progesterone.[24,25] However, LH levels during stimulation do not always correlate with progesterone elevation, contributing to inconsistent findings regarding their influence on clinical outcomes.[26]

While embryo quality and progesterone levels are important factors influencing pregnancy outcomes, our study suggests that low LH levels on the trigger day may also play a role, particularly in fresh embryo transfer cycles. Although low LH levels may not directly affect embryo quality, they can potentially impact endometrial receptivity. This could lead to increased rates of implantation failure and early pregnancy loss. In such cases, strategies such as freeze-all might be considered. Luo et al. found that low LH levels were associated with reduced live birth rates, but did not impact outcomes in freeze-all cycles.[14] It is important to note that the findings of this study are specific to normogonadotropic patients undergoing fresh embryo transfer cycles with no pathological progesterone levels on trigger day.

We acknowledge the limitations of this study, including the sample size and retrospective nature of the study. We carefully selected patients based on inclusion and exclusion criteria to mitigate potential confounding factors and adjusted our analysis for multiple variables. Another limitation was that the study involved a heterogeneous group of exogenous hormonal agents for COS. Furthermore, a limitation of current LH assays is their potential inaccuracy in measuring LH bioactivity.[27] And finally, this study was conducted in normogonadotropic patients with at least one available embryo. Our findings may not apply to the general population. Future prospective studies with larger sample sizes are needed to answer whether serum LH concentration can be utilized as a biomarker to optimize ovarian stimulation and embryo transfer outcomes.

CONCLUSION

The results of our study indicate that lower LH levels on the hCG trigger day are associated with decreased pregnancy and live birth rates. An LH threshold of 2.7 mIU/ml on the hCG trigger day can be used to predict unsuccessful pregnancy outcomes. Given the

potential risks associated with low LH levels, a freeze-all strategy might be a prudent approach. Discussing this option with the patient and weighing the potential benefits and drawbacks is essential.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Bülent Berker;* ***Design:*** *Bülent Berker, Şeyma Osmanlıoğlu;* ***Control/Supervision:*** *Bülent Berker;* ***Data Collection and/or Processing:*** *Şeyma Osmanlıoğlu, Koray Görkem Saçıntı;* ***Analysis and/or Interpretation:*** *Bülent Berker, Şeyma Osmanlıoğlu;* ***Literature Review:*** *Şeyma Osmanlıoğlu;* ***Writing the Article:*** *Şeyma Osmanlıoğlu, Bülent Berker;* ***Critical Review:*** *Bülent Berker.*

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