The Impact of Serum LH levels on the Day of hCG Trigger on IVF Outcomes in Patients Undergoing GnRH Antagonist Protocols

GnRH Antagonist Protokolleri Uygulanan Hastalarda hCG Tetikleme Günü Serum LH Düzeylerinin IVF Sonuçlarına Etkisi

Erhan Demirdag[1], Ismail Guler[1], M. Funda Cevher Akdulum[1], Cengiz Karakaya[2], Esin Sahin[1], Ahmet Erdem[1], Mehmet Erdem[1]

[1]Department of Obstetrics and Gynecology, Gazi University Faculty of Medicine, Emniyet Mahallesi, Gazeteci Yazar Muammer Yaşar Bostancı Sokak, 06560 Yenimahalle/Ankara, Turkey
[2]Department of Medical Biochemistry, Gazi University Faculty of Medicine, Emniyet Mahallesi, Gazeteci Yazar Muammer Yaşar Bostancı Sokak, 06560 Yenimahalle/Ankara, Turkey

ABSTRACT

Objective: To evaluate whether hCG day serum LH levels have an impact on IVF outcomes in patients undergoing GnRH antagonist protocols.
Methods: This retrospective cohort study was carried out in a private IVF clinic from September 2017 to January 2021. A total of 971 completed IVF cycles with GnRH antagonists were evaluated. Three groups with different LH levels were analysed according to hCG day serum LH concentrations: Group 1: LH ≥10 mIU/ml, Group 2: LH = 1.2-10 mIU/ml, and Group 3: LH <1.2 mIU/ml.
Results: Total dose of gonadotropin consumption was significantly higher, and the number of MII oocytes retrieved was significantly lower in group 3 than others (p<0.001). The maturation rates and implantation rates were significantly lower in group 3 compared to other groups (p<0.05, p<0.05, respectively). Clinical pregnancy (CPR) and live birth rates (LBR) per cycle were significantly lower in group 3 (6.2%, 6.2%, respectively) compared to group 1 (41.3%, 35.3, respectively) and group 2 (38.7%, 31.4%, respectively) (p<0.001, p<0.001, respectively). CPR and LBR per embryo transfer were also significantly lower in group 3 than others (p=0.003, p=0.029, respectively). Multivariate logistic regression analysis revealed that female age, number of MII oocytes retrieved, and serum hCG day LH levels were the significant variables in predicting live birth.
Conclusion: Higher hCG day LH levels result in poor pregnancy outcomes, especially in older poor responders, and GnRH antagonists seem ineffective in these patients. However, lower hCG day LH levels may not affect IVF outcomes in antagonist cycles.

Key Words: Luteinizing Hormone, Fertilization in Vitro, Ovulation Induction, Pregnancy Outcome, Gonadotropin-Releasing Hormone, Hormone Antagonists

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ÖZET

Amaç: GnRH antagonist protokolleri uygulanan hastalarda hCG tetikleme günü serum LH düzeylerinin IVF sonuçları üzerinde bir etkisi olup olmadığını değerlendirmek.
Yöntem: Bu retrospektif kohort çalışması, Eylül 2017 ve Ocak 2021 tarihleri arasında özel bir IVF kliniğinde gerçekleştirildi. Toplam 971 tamamlanmış GnRH antagonist IVF siklusu değerlendirildi. Farklı LH seviyelerine sahip üç grup, hCG günü serum LH konsantrasyonlarına göre analiz edildi: Grup 1: LH ≥10 mIU/ml, Grup 2: LH = 1.2-10 mIU/ml ve Grup 3: LH <1.2 mIU/ml.
Bulgular: Toplam gonadotropin dozu grup 3'te diğer gruplara göre anlamlı olarak daha yüksek iken toplanan MII oosit sayısı anlamlı olarak daha düşüktü (p<0.001). Matürasyon oranları ve implantasyon oranları grup 3'te diğer gruplara göre anlamlı derecede düşüktü (sırasıyla p<0.05, p<0.05). Siklus başına klinik gebelik ve canlı doğum oranları, grup 3'te (sırasıyla % 6.2, % 6.2) grup 1 (sırasıyla % 41.3, % 35.3) ve grup 2'ye (sırasıyla %38.7, %31.4) kıyasla anlamlı olarak daha düşüktü (sırasıyla p<0.001, p<0.001). Embriyo transferi başına klinik gebelik ve canlı doğum oranları da grup 3'te diğer gruplara göre anlamlı derecede daha düşüktü (sırasıyla p=0.003, p=0.029). Çok değişkenli lojistik regresyon analizi, kadın yaşı, toplanan MII oosit sayısı ve serum hCG günü LH düzeylerinin canlı doğumu öngörmede önemli değişkenler olduğunu ortaya koydu.
Sonuç: Human koryonik gonadotropin tetikleme günündeki yüksek düzeydeki LH seviyeleri, özellikle yaşlı ve zayıf yanıt veren hastalarda kötü gebelik sonuçlarıyla sonuçlanmaktadır ve GnRH antagonistleri bu hastalarda etkisiz görünmektedir. Bununla birlikte, düşük hCG günü LH seviyeleri, antagonist sikluslarda IVF sonuçlarını etkilemeyebilir.

Anahtar Sözcükler: Luteinizan Hormon, İnvitro fertilizasyon, Ovulasyon İndüksiyonu, Gebelik Sonucu, Gonadotropin Salgılatıcı Hormon, Hormon Antagonistleri

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ORCID IDs: E.D.0000-0003-4599-3854,I.G.0000-0002-8098-2483,C.K.0000-0002-0399-9150,E.S.0000-0002-6509-1949,M.F.C.A.0000-0003-2285-7112,A.E.0000-0001-9944-6894,M.E.0000-0002-1939-7138

Address for Correspondence / Yazışma Adresi: Erhan Demirdag, MD Department of Obstetrics and Gynecology, Gazi University Faculty of Medicine, Emniyet Mahallesi, 06560 Yenimahalle,Ankara, Turkey E-mail: edemirdag@gazi.edu.tr

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INTRODUCTION

Luteinizing hormone (LH) is a crucial gonadotropin in folliculogenesis through androgen production from theca cells and plays a critical role in ovulation triggering in the late follicular phase (1). Although follicle-stimulating hormone (FSH) is sufficient for follicular growth, LH is required for oocyte maturation and endometrial preparation that provides proper implantation (2).

The importance of LH levels for optimal follicular development and maturation during controlled ovarian hyperstimulation (COH) has been investigated in the literature. It has been stated that while lower LH levels result in abnormal oocyte maturation, higher LH levels lead to poor pregnancy outcomes due to premature LH surge (3).

In COH cycles, suppression of LH is a critical phase to achieve favorable IVF outcomes. It has been shown that higher early follicular phase LH levels may lead to early luteinization of follicles resulting in follicular atresia during COH (4). Besides this, premature LH surge may cause early endometrial maturation that may negatively affect embryo implantation and pregnancy success (5). Although both GnRH agonists and antagonists can be used to inhibit premature LH surge in IVF protocols, GnRH antagonists have been generally preferred in recent years since their rapid effect on LH levels and patients' convenience (6, 7). However, GnRH antagonists may profoundly suppress LH, and it was presented that profound LH suppression during ovarian stimulation may also result in poor IVF outcomes due to the low oocyte yields and abnormal endometrial receptivity (8, 9). Thus, the balance of LH levels in the optimal range is thought to be important in COH protocols to improve IVF outcomes.

It has been shown that fewer than 1% occupied LH receptors is enough for optimal steroidogenesis (1). However, optimal LH levels have not been identified yet in COH cycles. Although optimal LH range has been defined as 1.2-5.0 IU/L in some studies (7, 10), there is a lack of information in the literature about whether the LH levels on the day of ovulation trigger have an impact on IVF outcomes in GnRH antagonist cycles. Considering the importance of LH on follicle development, final oocyte maturation, and pregnancy outcomes, it could also be useful to evaluate the LH levels on the day of ovulation trigger for counseling patients about IVF treatment success.

For this reason, we aimed to evaluate how hCG trigger day LH levels affect IVF outcomes in patients undergoing GnRH antagonist IVF protocol in this study.

METHODS

Study population and study design

This observational cohort study was conducted retrospectively between September 2017 and January 2021 at a private infertility clinic (Novaart IVF Center) in Ankara. All IVF/ICSI cycles with GnRH antagonist protocol were reviewed from the medical records of the clinic. All completed GnRH antagonist protocol IVF cycles were included in the study. Patients with previous intrauterine or ovarian surgery, thaw cycles, and diagnosed with severe male factor infertility, autoimmune diseases, antiphospholipid antibody syndrome were excluded from the study. Three groups were formed according to LH levels on the day of hCG injection: Group 1: LH ≥10 mIU/ml, Group 2: LH = 1.2-10 mIU/ml, and Group 3: LH <1.2 mIU/ml. The lower limit of LH (<1.2 mIU/ml) was accepted according to described LH deficiency in the literature (11). The upper limit of LH (≥10 mIU/ml) was determined according to predefined premature LH surge levels (12).

Serum LH, estradiol, and progesterone measurements were performed in the morning on the day of hCG trigger. LH levels were measured by a chemiluminescent immunoassay kit (Beckman Coulter Access Immunoassay Systems, California) at the biochemistry laboratory of Gazi University Faculty of Medicine. All measurements were performed according to the manufacturer's instructions. The detection limit for the LH assay is 0.2 mIU/ml. The intraassay and interassay coefficients of variation with LH concentrations of 4.01 mIU/ml for the LH assays were 3.8% and 6.4%, respectively.

This study was approved by the Local Ethics Committee of Gazi University Faculty of Medicine (Number: E-77082166-604.01.02-61240).

Ovarian stimulation protocol

Patients' age, basal hormone levels, and antral follicle counts (AFC) were determined on the 3rd day of the cycle. The ovarian stimulation was performed with exogenous gonadotropins, including both recFSH (Gonal-F, Merck Serono, Turkey) and hMG (Menogon, Ferring, Turkey, or Merional, IBSA, Turkey) in all patients. Follicular growth was followed with serial transvaginal ultrasound examination and serum estradiol (E2) measurements to determine ovarian gonadotropin response and to adjust gonadotropin dose. Flexible GnRH antagonist protocol with 0.25 mg/day subcutaneous (SC) GnRH antagonist cetrorelix (Cetrotide; Merck Serono, Turkey) was used in all patients when the leading follicle ≥13 mm or E2 level >300 pg/mL and continued until the day of hCG trigger. When the mean diameter of at least two leading follicles was ≥18 mm, 250 µg of SC recombinant hCG (choriogonadotropin alfa) (Ovitrelle, Merck Serono, Turkey) was administered for final oocyte maturation. Transvaginal ultrasonography (TVU) guided oocyte pick-up (OPU) was performed 36 hours after hCG triggering. ICSI procedure was used to fertilize all retrieved metaphase II (MII) oocytes. Embryos were evaluated according to their morphology and cell number to determine top-quality embryos (TQE) for transfer. Grade 1-2 eight-cell blastomere embryos (grade I [high- quality]: embryos with equal blastomere and no observed cytoplasmic fragmentation; grade II [good-quality]: embryos with or without equal blastomere and <20% fragmentation of the cytoplasm) were defined as TQE. (13). Embryo transfer (ET) was performed with one to two TQE 3 or 5 days after oocyte retrieval under the transabdominal ultrasonographic guidance using a flexible catheter (Wallace; Irvine Scientific, Santa Ana, CA).

Vaginal progesterone was supplemented (Crinone 8% gel, Serono) to support the luteal phase after the OPU and continued until determining fetal heart activity. Clinical pregnancy was defined when a gestational sac or a fetus with cardiac activity was observed with ultrasonography. The live birth was accepted as the delivery of ≥23 weeks' gestation of a viable fetus.

Outcome measures

Primary outcome measures were clinical pregnancy rates (CPR), live birth rates (LBR), and implantation rates (IR) in this study. Secondary outcome measures were the number of oocytes retrieved (NOR), the number of mature oocytes, fertilization rates, and maturation rates (MR). Maturation rate was defined as the ratio of the total number of metaphase II (MII) oocytes to the total number of oocytes retrieved. Fertilization rate was determined as the ratio of the total number of fertilized oocytes to the total number of mature oocytes retrieved. Implantation rate was defined as the ratio of the total number of the gestational sac to the total number of embryos transferred. Poor response to gonadotropins was determined when the number of oocytes retrieved ≤5 after stimulation.

Statistical analysis

Data analysis was performed by Statistical Package for Social Sciences (SPSS, version 21.0, Statistics, 2013, Chicago, IBM, USA). Normality tests, including visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov test), were used to determine whether variables were normally distributed or not. Normally distributed parametric data were compared by "One-way analyses of variance" (One-way ANOVA) with Bonferroni post hoc test. Mann-Whitney U test was performed for comparison of non-normally distributed metric data. Categorical data were analyzed by Chi-square test. Data were expressed as mean ± standard deviation (SD) or percentages. Multivariate logistic regression analysis was used to determine variables to predict live birth and LH levels ≥10 mIU/ml. Cycle numbers and poor response to gonadotropins were used as categorical covariates in the multivariate logistic regression analysis. The model fit was assessed by Hosmer-Lemeshow goodness of fit statistics. Statistical significance was accepted as p <0.05.

RESULTS

A total of 971 completed GnRH antagonist cycles were analyzed for this study. There were 167 cycles in group 1, 739 cycles in group 2, and 65 cycles in group 3. OPU was not performed in 9 cycles of Group 3 and 2 cycles of Group 2 due to premature ovulation.

Comparison of baseline characteristics and IVF outcomes were presented in table 1. The mean age was significantly higher in group 3 (37.5 ± 4.6) as compared to group 1 (32.0 ± 4.8) and 2 (32.8 ± 5.6) (p<0.001). The mean AFC was significantly lower in group 3 (5.5 ± 5.3) than group 1 (12.7 ± 5.3) and 2 (12.3 ± 6.8) (p<0.001). Patients in group 3 used a significantly higher total dose of gonadotropins (3236.9 ± 1336.2) as compared to groups 1 and 2 (2631.8 ± 738.3, 2755.3 ± 796.1, respectively) (p<0.001). The mean number of MII oocytes retrieved (2.4 ± 4.3) was significantly lower in group 3 than group 1 (8.8 ± 4.2) and group 2 (8.1 ± 5.6) (p<0.001). The MR and IR were significantly lower in group 3 (70.9%, 8.9%, respectively) compared to group 1 (79.3%, 29.1%, respectively) and 2 (77.5%, 27.2%, respectively) (p<0.05, p<0.05, respectively). Poor response to gonadotropins was significantly higher in group 3 (89.2%) than in other groups 1 and 2 (13.8%, 24.8%, respectively) (p<0.001).

CPR and LBR per cycle were significantly lower in group 3 (6.2%, 6.2%, respectively) compared to group 1 (41.3%, 35.3, respectively) and group 2 (38.7%, 31.4%, respectively) (p<0.001, p<0.001, respectively). CPR and LBR per ET were also significantly lower in group 3 (12.5%, 12.5%, respectively) compared to group 1 (42.3%, 36.2, respectively) and group 2 (42.8%, 34.7%, respectively) (p=0.003, p=0.029, respectively).

Multivariate logistic regression analyses to predict live birth were shown in table 2. Female age, number of MII oocytes retrieved, and serum LH levels on the trigger day of hCG were found as significant variables in predicting live birth (OR: 0.959, CI: 0.931-0.987, p<0.05, OR: 1.137, CI: 1.047-1.235, p<0.05, OR: 0.945, CI: 0.900-0.992, p<0.05, respectively). In addition, multivariate logistic regression analysis revealed that female age (OR: 1.089, CI: 1.024-1.158, p<0.05) and poor response to gonadotropins (OR: 15.734, CI: 4.569-54.182, p<0.001) were significant variables for prediction of LH levels ≥10 mIU/ml.

Table 1. Comparison of baseline characteristics and IVF outcomes between groups

Variables (971 cycles)	Group of LH levels <1.2 mIU/mL [(1)] (167 cycles)	Group of LH levels between 1.2-10 mIU/mL [(2)] (739 cycles)	Group of LH levels ≥10 mIU/mL [(3)] (65 cycles)	*P*-value
Age (years)	32.0 ± 4.8 [(3)]	32.8 ± 5.6 [(3)]	37.5 ± 4.6 [(1,2)]	<0.001
BMI (kg/m^2)	22.2 ± 2.1	21.9 ± 2.0	22.4 ± 1.9 [(2)]	0.137
Basal FSH (mIU/ml)	5.7 ± 3.3 [(3)]	6.9 ± 3.5	8.7 ± 4.0 [(1)]	0.009
Basal E_2 (pg/ml)	38.8 ± 18.9	41.4 ± 31.3	38.4 ± 33.5	0.458
Antral follicle count	12.7 ± 5.3 [(3)]	12.3 ± 6.8 [(3)]	5.5 ± 5.3 [(1,2)]	<0.001
Duration of infertility (years)	5.0 ± 3.6	5.5 ± 4.4 [(3)]	5.0 ± 4.3	0.366
Total dose of gonadotropins (IU)	2631.8 ± 738.3 [(3)]	2755.3 ± 796.1 [(3)]	3236.9 ± 1336.2 [(1,2)]	<0.001
Serum E_2 on the day of hCG injection (pg/ml)	2975.2 ± 1581.7 [(3)]	2833.5 ± 1989.2 [(3)]	966.8 ± 961.7 [(1,2)]	<0.001
Serum P on the day of hCG injection (ng/ml)	1.0 ± 0.6	0.9 ± 0.5	0.9 ± 0.7	0.259
Number of ≥17 mm follicle count on the day of hCG injection	4.6 ± 2.1 [(3)]	4.3 ± 2.3 [(3)]	2.1 ± 1.7 [(1,2)]	<0.001
Endometrial thickness at the day of hCG injection (mm)	11.1 ± 1.9	11.3 ± 2.1 [(3)]	10.6 ± 1.8 [(2)]	0.028
Number of total oocytes retrieved	11.1 ± 5.0 [(3)]	10.4 ± 6.4 [(3)]	3.4 ± 5.9 [(1,2)]	<0.001
Number of MII oocytes retrieved	8.8 ± 4.2 [(3)]	8.1 ± 5.6 [(3)]	2.4 ± 4.3 [(1,2)]	<0.001
Fertilization rates (%)	75.7	73.1	72.8	0.114
Maturation rates (%)	79.3 [(3)]	77.5 [(3)]	70.9 [(1,2)]	0.012
Implantation rates (%)	29.1 [(3)]	27.2 [(3)]	8.9 [(1,2)]	0.017
Number of transferred embryos	1.9 ± 0.5 [(3)]	2.0 ± 0.6 [(3)]	1.4 ± 0.5 [(1,2)]	<0.001
Poor response to gonadotropins (%)	13.8 [(2,3)]	24.8 [(1,3)]	89.2 [(1,2)]	<0.001
Clinical pregnancy rate, per cycle, n (%)	69 (41.3) [(3)]	286 (38.7) [(3)]	4 (6.2) [(1,2)]	<0.001
Live birth rate, per cycle, n (%)	59 (35.3) [(3)]	232 (31.4) [(3)]	4 (6.2) [(1,2)]	<0.001
Clinical pregnancy rate, per embryo transfer, n (%)	69 (42.3) [(3)]	286 (42.8) [(3)]	4 (12.5) [(1,2)]	0.003
Live birth rate, per embryo transfer, n (%)	59 (36.2) [(3)]	232 (34.7) [(3)]	4 (12.5) [(1,2)]	0.029

Data were presented as mean ± SD, numbers, and percentages. BMI: Body mass index; FSH: Follicle-stimulating hormone; E_2: Estradiol; LH: Luteinizing Hormone, P: Progesterone; hCG: Human chorionic gonadotropin. MII: Metaphase 2. Statistically significant differences between groups were presented with Superscript [(n)]; p <0.05 was considered significant.

Table 2. Multivariate logistic regression analyses of variables to predict live birth

Variables	Live Birth Odds Ratio	95% Confidence İnterval	*P*-value
Age	0.959	0.931-0.987	0.005
Antral follicle count	0.979	0.910-1.054	0.579
Number of total oocytes retrieved	0.964	0.873-1.064	0.463
Number of Metaphase II oocytes retrieved	1.137	1.047-1.235	0.002
Total dose of gonadotropins	1.000	1.000-1.000	0.303
Number of ≥17 mm follicle count on the day of hCG injection	1.008	0.937-1.084	0.836
Serum LH on the day of hCG injection	0.945	0.900-0.992	0.022
Cycle number [(a)]			0.483

Variable with Superscript [(a)] was selected as the categorical covariate.

DISCUSSION

In the present study, we found that NOR, the number of MII oocytes retrieved, MR, IR, CPR, and LBR were significantly lower in the group with LH levels ≥10 mIU/ml. However, these outcomes were similar among lower and normal LH levels groups. The impact of LH levels on the day of ovulation triggering in patients undergoing IVF treatment with GnRH antagonists is not clearly clarified despite the well-known importance of LH on folliculogenesis. Although some LH levels were determined in the literature for favorable IVF outcomes (2, 7, 9, 14), there is still debate especially regarding the lower level of LH.

Luteinizing hormone (LH) elevation is accepted to be an important problem during COH cycles. It may negatively affect oocyte development and is associated with poor pregnancy outcomes (5, 15). In our results, the lowest pregnancy and cycle outcomes were found in the group with LH ≥10 mIU/ml, which was in line with previous reports. Besides this, female age and poor response to gonadotropins were found as significant variables in predicting LH higher than 10 mIU/ml in this study. Late follicular phase LH surge causing premature luteinization of the oocytes and premature endometrial maturation that leads to abnormal milieu for implantation may explain these poor outcomes. Our results could also be explained by higher LH tonus in older poor responder patients despite the GnRH antagonist administration. This relationship was also pointed out by another study in which premature LH surge was higher, and GnRH-anta was less effective in patients with increased age and poor ovarian reserve (16).

A possible problem in using the GnRH antagonist protocol may be the profound suppression of LH. The threshold value was accepted as LH <1.2 mIU/ml in our study due to the defined suppressed LH concentrations in hypogonadotropic hypogonadism patients (11). Although there are some studies about the effect of LH suppression on IVF outcomes, existing data is controversial especially regarding the GnRH anta cycles. In our research, we found similar IR, MR, CPR, and LBR among the group with LH levels <1.2 mIU/ml and the group with LH levels 1.2-10 mIU/ml. Chen et al. defined the low LH group as LH levels ≤0.8 mIU/ml in their IVF cycles and found similar IR, CPR, and LBR between the study group with LH levels ≤0.8 mIU/ml and control group with LH levels ≥0.8 mIU/ml. They assessed the association between low LH levels and early pregnancy loss, including the loss of clinical pregnancy with or without fetal cardiac activity in that study, and reported significantly higher early pregnancy loss rates in patients with LH levels ≤0.8 mIU/ml (2). Unlike this study, the early pregnancy loss rate was similar among our lower and normal LH groups (12.6%, 12.9%, respectively). Propst et al. investigated the impact of low LH levels on IVF outcomes after GnRH-anta administration. They used a threshold of 0.5 mIU/ml LH in that study and reported lower implantation and pregnancy rates in patients with LH levels ≤0.5 mIU/mL (9). However, Merviel et al. found that LH concentrations ≤0.5 mIU/ml on the day of hCG injection did not negatively affect follicular maturation, pregnancy outcomes (14). The different threshold levels of LH could explain these controversial results in these studies. In fact, the lower limit of LH concentration is still unknown, although the evidence shows that LH is required for follicular maturation and adequate steroidogenesis. Thus, it can be speculated that LH concentrations below these mentioned thresholds might be enough for favorable pregnancy outcomes in IVF with GnRH antagonist protocols.

We found that age, the number of metaphase II oocytes retrieved, and serum LH on the day of hCG injection were significant variables in predicting live birth. However, it was found in a study that although hCG day LH was negatively correlated with NOR, there was no significant correlation between hCG day LH and favorable pregnancy outcomes (17). According to our results, it can be speculated that hCG day LH may become more crucial in older women. Considering the association between elevated LH levels and follicular atresia (18), higher hCG day LH concentrations may further worsen mature oocyte yield, especially in older poor responder patients, and decreased IVF success, although GnRH antagonist administration.

The main strength of our study is the large sample size of IVF cycles with GnRH antagonists. Another strength is the comparison of three different groups of LH levels on the day of hCG injection. The major limitations of the study are retrospective design and bias potential of medical records.

In conclusion, higher serum LH concentration on the day of hCG trigger is associated with poor pregnancy outcomes in IVF treatment, and GnRH antagonists may not be effective in patients with advanced age due to the poor response to gonadotropins.

However, it seems that lower LH levels on the day of hCG trigger might be an insignificant factor for favorable pregnancy outcomes in antagonist IVF cycles.

Conflict of interest

No conflict of interest was declared by the authors.

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REFERENCES

1.Rashidi BH, Kabodmehri R, Shariat M, Tehraninejad ES, Abdollahi A, Bagheri M, et al. Luteinizing hormone changes in gonadotropin-releasing hormone antagonist protocol in in vitro fertilization cycles: A cross-sectional study. International Journal of Reproductive BioMedicine. 2019;17(3):209.

2.Chen C-D, Chiang Y-T, Yang P-K, Chen M-J, Chang C-H, Yang Y-S, et al. Frequency of low serum LH is associated with increased early pregnancy loss in IVF/ICSI cycles. Reproductive biomedicine online. 2016;33(4):449-57.

3.Wiweko B, Pradipta B, Natadisastra M, Sumapraja K, Mansyur E, Yuningsih T, et al. The Association Between LH Serum Levels at the time of hCG Injection and Clinical Pregnancy during IVF. eJournal Kedokteran Indonesia. 2015.

4.Diedrich K, Diedrich C, Santos E, Zoll C, Al-Hasani S, Reissmann T, et al. Suppression of the endogenous luteinizing hormone surge by the gonadotrophin-releasing hormone antagonist Cetrorelix during ovarian stimulation. Human Reproduction. 1994;9(5):788-91.

5.Ramachandran A, Jamdade K, Kumar P, Adiga SK, Bhat RG, Ferrao SR. Is there a need for luteinizing hormone (LH) estimation in patients undergoing ovarian stimulation with gonadotropin-releasing hormone (GnRH) antagonists and recombinant follicle-stimulating hormone (rFSH)? Journal of clinical and diagnostic research: JCDR. 2014;8(1):90.

6.Huirne JA, Van Loenen AC, Schats R, McDonnell J, Hompes PG, Schoemaker J, et al. Dose-finding study of daily GnRH antagonist for the prevention of premature LH surges in IVF/ICSI patients: optimal changes in LH and progesterone for clinical pregnancy. Human reproduction. 2005;20(2):359-67.

7.Liu M, Liu S, Li L, Wang P, Li H, Li Y. LH levels may be used as an indicator for the time of antagonist administration in GnRH antagonist protocols—a proof-of-concept study. Frontiers in endocrinology. 2019;10:67.

8.Fleming R, Lloyd F, Herbert M, Fenwick J, Griffiths T, Murdoch A. Effects of profound suppression of luteinizing hormone during ovarian stimulation on follicular activity, oocyte and embryo function in cycles stimulated with purified follicle stimulating hormone. Human reproduction (Oxford, England). 1998;13(7):1788-92.

9.Propst AM, Hill MJ, Bates GW, Palumbo M, Van Horne AK, Retzloff MG. Low-dose human chorionic gonadotropin may improve in vitro fertilization cycle outcomes in patients with low luteinizing hormone levels after gonadotropin-releasing hormone antagonist administration. Fertility and sterility. 2011;96(4):898-904.

10. Raju GAR, Chavan R, Deenadayal M, Gunasheela D, Gutgutia R, Haripriya G, et al. Luteinizing hormone and follicle stimulating hormone synergy: a review of role in controlled ovarian hyper-stimulation. Journal of human reproductive sciences. 2013;6(4):227.

11.O'Dea L, O'Brien F, Currie K, Hemsey G. Follicular development induced by recombinant luteinizing hormone (LH) and follicle-stimulating hormone (FSH) in anovulatory women with LH and FSH deficiency: evidence of a threshold effect. Current medical research and opinion. 2008;24(10):2785-93.

12. Depalo R, Trerotoli P, Chincoli A, Vacca MP, Lamanna G, Cicinelli E. Endogenous luteinizing hormone concentration and IVF outcome during ovarian stimulation in fixed versus flexible GnRH antagonist protocols: An RCT. International Journal of Reproductive BioMedicine. 2018;16(3):175.

13. Hardarson T, Hanson C, Sjögren A, Lundin K. Human embryos with unevenly sized blastomeres have lower pregnancy and implantation rates: indications for aneuploidy and multinucleation. Human Reproduction. 2001;16(2):313-8.

14. Merviel P, Antoine J-M, Mathieu E, Millot F, Mandelbaum J, Uzan S. Luteinizing hormone concentrations after gonadotropin-releasing hormone antagonist administration do not influence pregnancy rates in in vitro fertilization–embryo transfer. Fertility and sterility. 2004;82(1):119-25.

15. Marci R, Graziano A, Lo Monte G, Piva I, Soave I, Marra E, et al. GnRH antagonists in assisted reproductive techniques: a review on the Italian experience. Eur Rev Med Pharmacol Sci. 2013;17(7):853-73.

16. Kochhar PK, Ghosh P. Diminished ovarian reserve predisposes to premature luteinizing hormone surges in gonadotropin-releasing hormone antagonist cycles in In vitro fertilization. Journal of Human Reproductive Sciences. 2020;13(3):191.

17. Wang A-C, Wang Y, Wu F-X, Zhu D-Y. Assessing predictors for the success of GnRH antagonist protocol in reproductive women in IVF/ICSI-in fresh cycles. Biomedical reports. 2017;7(5):482-6.

18. Shoham Z. The clinical therapeutic window for luteinizing hormone in controlled ovarian stimulation. Fertility and Sterility. 2002;77(6):1170-7.