

Luteinizing Hormone Levels as an Indicator of the Timing of Antagonist Administration in a Gonadotropin-Releasing Hormone Antagonist Protocol

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ABSTRACT

Background & Objective: Gonadotropin-releasing hormone acts on the anterior pituitary and promotes the release of both follicle-stimulating hormone (FSH) and luteinizing hormone (LH), both of great importance in the ovarian cycle.

Materials & Methods: In a prospective cross-sectional study conducted at the High Institute for Infertility Diagnosis and Assisted Reproductive Technologies / Al-Nahrain University and Kamal Al-Sameraie Hospital for Infertility and In Vitro Fertilization, Baghdad, Iraq during the period from April 2022 to April 2023, women received rFSH in a single daily dose of (150-300 IU) for ovarian stimulation. Women in groups B and C received ovarian stimulation antagonists, while those in group A did not.

Results: Both clinical and ongoing pregnancy rates were measured for each group. A positive hCG test was found in 27 (79.4%) in Group A while it was positive in 19 (55.9%) in Group B with a significant difference (P=0.03), clinical pregnancy was 25 (73.5%) in Group A while it was positive in 17 (50.0%) in Group B with a significant difference (P=0.04), and ongoing pregnancy was found in 24 (70.6%) in Group A while it was positive in 15 (44.1%) in Group B with significant difference (P=0.01).

Conclusion: Women with LH <4 IU presented with a significantly higher pregnancy rate than those with ≥4 IU, and do not need GnRH antagonist addition as co-treatment.

Keywords: Infertility, Luteinizing Hormone, Mineralocorticoid Receptor Antagonists, Pregnancy rate, Gonadotropin-Releasing Hormone



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Introduction

Infertility is one of the major problems in society, which sometimes endangers the continuity of family life in the long term. About 30-40% of the causes of infertility in women are related to ovarian disorders, and the rest are related to uterine disorders, immune factors, and systemic diseases (1, 2). So, it is an important issue to investigate the hormonal disorder in cases with this problem. The synthesis of luteinizing hormone starts in the pituitary gland as soon as the female has reached sexual maturity with the onset of the first menstrual cycle. Its synthesis is controlled by gonadotropin-releasing hormone (GnRH) in reaction to other stimuli. At the beginning of a woman's menstrual cycle, the luteinizing hormone is at basal levels. As estrogen levels rise due to the growth of ovarian follicles, LH receptors begin to express themselves in their cells. Lastly, when a pre-ovulatory or Graafian follicle has developed and is prepared to mature and estrogens are very high, the continuous release of LH is made active over a period of 24 to 48 hours (3).

In recent decades, growing knowledge about ovarian physiology and the ability to accurately assess ovarian reserve have gradually steered toward the individualization of ovarian stimulation adaptation for in vitro fertilization management. A sudden clampdown of luteinizing hormone (LH) occurs throughout the controlled ovarian stimulus, which is important for attaining relevant results from assisted reproductive technology. The protocols of assisted reproduction techniques using GnRH agonists were considered the reference standard of the last two decades; GnRH antagonists offer control of the endogenous surge of luteinizing hormone in a faster and more suitable way (4).

The direct inhibition of GnRH was caused by antagonists with no flaring up effect, whereas the action of agonists is done over down regulation, and the antagonists precisely act to block GnRH receptors and encourage reduced serum LH concentrations and a less pronounced drop in the secretion of follicular

stimulating hormone. The apparent result is low concentrations of both luteinizing hormone and follicular stimulating hormone (5).

In the last few years, it has been found that GnRH antagonists are suitable for the fast and reversible destruction of releasing luteinizing hormone. It is recommended to use a gonadotropin-releasing hormone antagonist protocol along with a GnRH agonist trigger and freezing to prevent Ovarian disease and hyperstimulation syndrome (OHSS) (6).

The starting day of GnRH antagonist administration in conventional GnRH antagonist protocols (i.e. both fixed and flexible protocols) is mainly based on the day of ovarian stimulation, follicle diameter, estradiol level, or a combination of these parameters. Alternatively, the day of initiation of GnRH antagonist treatment can also be chosen at random (7). These methods try to prevent an increase in endogenous LH levels, rather than taking into account the LH levels that are present throughout the growth of the follicles. LH is necessary for the development of mature oocytes and the maintenance of healthy follicles (8). In particular, LH can stimulate the proliferation and differentiation of theca cells, which leads to an increase in the release of androgens. These androgens are amplified synergistically by the creation of estrogen (9). During the late follicular phase, LH produces a modest quantity of progesterone. This, in turn, makes a contribution to the positive feedback that estrogens provide, which is essential for the growth and development of follicles (10).

Many researchers have suggested that there is a "window for luteinizing hormone clinical management space," in which the levels of this hormone are more significant than the "LH ceiling" which is linked with the abnormal development of follicles (11). Recently, the regimen of GnRH antagonists has been extensively used in IVF treatments (12).

There is a considerable variation among individuals concerning both the excretion and the response of luteinizing hormone levels to antagonists. The purpose of the antagonistic regimen is to overwhelm specific physiological processes, explicitly inhibiting the rapid rise in luteinizing hormone. Consequently, the early beginning of ovulation is the desired outcome (13). On the other hand, in particular for women, endogenous LH levels are insufficient to promote follicular development ultimately; such women may not necessarily need an antagonist regimen (14). Even though several revisions have shown that LH levels must be in a range of 1.2-5.0 IU/L for best follicular development (15). The main objective of this research is to determine whether luteinizing hormone levels can be used as an indicator to add antagonists to the gonadotropin hormone antagonist protocol.

Methods

A prospective cross-sectional study was conducted at the High Institute for Infertility Diagnosis and Assisted Reproductive Technologies / Al-Nahrain University and Kamal Al-Sameraie Hospital for Infertility and In Vitro Fertilization, Baghdad, Iraq from April 2022 to April 2023 (ethical code: 123:2022-05-22). After approval by the local committee of the Arab Board of Obstetrics and Gynecology in Iraq, written consent was obtained from each patient after a detailed explanation of the purpose of the study. Women aged less than 40 years old with a level of FSH below 12 IU/L were enrolled. Patients were excluded if they had one or more of the following: uterine polyp, endometriosis, adhesion, müllerian anomaly, adenomyosis, or adnexal anomaly. The normal amount of LH in women depends on which phase of the menstrual cycle they are in (16):

Follicular phase, or early in the menstrual cycle: 15–68 IU/L

Mid-cycle, or near mid-cycle: 56.6–9 IU/L

Luteal phase, which is the end of the cycle: 16.3–61 IU/L

In women and in menopause, the normal amount of LH is equal to: 14.2-52.3 IU/L.

If the person is not ovulating and the LH level is still higher than normal, the person may be in menopause. High levels of LH also indicate problems with the pituitary gland and polycystic ovary syndrome. If the LH level is lower than normal, it may be for the following reasons: malnutrition, anorexia nervosa, stress, and pituitary problems.

The study included 102 women and was assigned into three equal groups with 34 women in each, according to their luteinizing hormone levels during controlled ovarian stimulation and prescription of a GnRH antagonist or no.

The first group included women whose LH level was less than 4 IU/L and had not received an antagonist, namely Group A.

The second group included those women whose LH was less than 4 IU/L with the addition of antagonist as co-treatment.

The third group included women with an LH level of 4 IU/L or more in addition to the antagonists as co-treatment.

Stimulation Protocol

rFSH was administered as a single daily dose of (150–300 IU) to the women. Starting on day two of the cycle, the women were given a single daily dose of (150–300 IU) rFSH to stimulate their ovaries. The levels of both estradiol and luteinizing hormone in serum were assessed after four to five days, in addition to performing an ultrasound on the women. The

amount of gonadotropin administered was modified in response to changes in hormone levels and the progression of follicular growth. At least three separate hormone tests were performed throughout the control ovarian stimulation, and the results were as stated below:

Day two of stimulation, four-five days after stimulation, and on the trigger day

In the meantime, luteinizing hormone levels were checked frequently during the whole period of control ovarian stimulation; a modified flexible antagonist protocol was used in this study based on luteinizing hormone levels in some women. For women with $(LH < 4 \text{ IU/L})$, no antagonist administration was necessary, while for those with $(LH \geq 4 \text{ IU/L})$, for a duration of two days, cetrorelix acetate in a dose of 0.25 milligrams was administered until the time of the subsequent blood investigation. The choice to remain antagonistic as co-treatment was based on consequent luteinizing hormone results of more than 4 IU/L until the triggering day .

Women in the "A" and "C" groups received personalized labeling strategies, while women in the "B" group were stimulated using a flexible antagonist regimen. The administration of the antagonist began on the day that the estradiol level reached 400pg/ml or the dominant follicle diameter reached 14 mm, and it lasted until the day that the stimulation of the LH level below 4 IU/L began. On this day, the women were considered to have attained their maximum potential for pregnancy.

The beginning of the final maturation of the oocyte occurred when the primordial follicle was detected to be 18-20 mm or > 3 follicles of 16 mm. 0.2 mg of triptorelin plus 1000-2000 international units of human gonadotropin were administered for this. Egg extraction was performed after 36 hours.

Embryo Transfer and Luteal Phase Support

Three days afterward, oocyte retrieval and the fresh embryo transformation were completed. To support the luteal phase, we gave the women oral tablets of dydrogesterone in a dose of 10mg twice a day, in addition to a gel of vaginal progesterone. While all procedures were, frizzing for women presented with a high risk of ovarian hyperstimulation syndrome or those with serum progesterone levels greater than 1.5 ng/ml throughout controlled ovarian stimulation and those with an ET less than 7mm.

In such cases, during day three, two good-quality embryos were vitrified, and 2-3 days, we cultured the residual embryos for blastocyst verification.

In the beginning, we transferred only day three embryos, and this transfer of frozen-thawed embryos was done by using either an artificial cycle or a regular cycle .

Temporarily, women were administered oral estradiol valerate at 6 mg/24 hrs for 10 to 12 days starting from day two of MC. This was done for artificial endometrial preparation, then we assessed the endometrial thickness by vaginal US, and the progesterone was administered as in fresh cycles when the thickness of endometrium was equal to or greater than 8 mm, and after four days, the embryo was transferred.

Regarding the natural cycles, since day 12 of MC, we have checked follicular development, and three days after ovulation, we performed embryo transfer. Then, after 12-14 days, we studied serum human chorionic gonadotropin levels.

As soon as the pregnancy happened, the luteal phase support was sustained for about nine to ten weeks after conception.

Statistical Analysis

The analyses were performed statistically using the Statistical Package for the Social Sciences (SPSS) version 25 (IBM, USA) and the data in this study were stated as the mean \pm standard deviation (SD). We used both the independent sample t-test and the Mann-Whitney U-test to compare continuous parameters with either normal or non-normal distributions. The chi-square test is used to compare frequencies and categorical variables. Level of significance: The P value was set at ≤ 0.05 to be considered statistically significant.

Results

A total of 102 women were included in the current study and distributed according to the levels of LH into three groups during control ovarian stimulation and whether gonadotropin antagonists were given.

Baseline, hormonal, and cycle criteria between Groups A and B

In the present study, 68 women presented with a low level of LH ($< 4 \text{ IU/L}$). Of these, 34 did not receive any antagonist, but the level of LH was $< 4 \text{ IU/L}$ (Group A), and the other 34 women had the same level of LH ($< 4 \text{ IU/L}$) but received a flexible protocol of antagonist (Group B). The LH level test in urine can be used to determine the time of ovulation. When LH levels begin to rise, this can indicate that ovulation is likely to occur within a day or two. These types of tests can be done at home and are often used to increase the chances of getting pregnant. It should be noted that this is done with a urine test.

No significant differences were found between the studied groups among baseline, hormonal, and cycle criteria ($P > 0.05$), regarding the differences in the hormonal assay and cycle characteristics between both groups, we noticed that there are no statistical differences between each of these parameters ($P > 0.05$), ([Table 1](#)).

Table 1. Differences between Group A and B among baseline, hormonal, and cycle criteria.

| Variables (Mean± SD) | Group A (n=34) LH <4 IU/L | Group B(n=34) LH <4 IU/L (and the antagonist) | P value |
|--------------------------------|---------------------------|---|---------|
| Age | 32.2 ± 3.7 | 31.9 ± 2.6 | 0.700 |
| BMI | 28.9 ± 4.3 | 28.4 ± 3.8 | 0.600 |
| Duration of infertility /years | 7.62±3.6 | 7.6±4.32 | 0.200 |
| Age of menarche | 12.14±1.18 | 12.14±0.78 | 0.90 |
| LH (IU/L) | 3.12±1.55 | 4.06 ± 2.61 | 0.07 |
| E2 (pg/ml) | 46.3±27.42 | 47.8±21.44 | 0.80 |
| GnRHa (IU) | 2471.1 ± 701.4 | 2408.0± 633.7 | 0.69 |
| FSH (IU/L) | 5.8±1.9 | 5.9±1.6 | 0.80 |
| Antral follicle count | 14.1± 6.4 | 14.8±5.7 | 0.60 |
| Duration of stimulation (day) | 9.9±1.3 | 9.7 ± 1.4 | 0.50 |
| ET on the day of hCG | 10.3 ± 2.4 | 9.9±2.1 | 0.46 |
| follicular output rate | 0.8 ± 0.3 | 0.89 ± 0.1 | 0.10 |
| Oocytes retrieved | 14.4 ± 8.6 | 15.5 ± 7.7 | 0.50 |
| MII Oocytes | 11.2 ± 7.5 | 11.8 ± 6.3 | 0.70 |
| High quality embryos | 4.4 ± 2.9 | 4.9 ± 2.3 | 0.43 |
| 2PN zygotes (no.) | 9.7 ± 6.9 | 9.5 ± 6.1 | 0.80 |

P. value < 0.05 (significant), LH= luteinizing hormone, E2= Estradiol, GnRHa= gonadotropin releasing hormone agonist, FSH= follicular stimulating hormone, ET= Endometrial thickness, 2PN zygotes= 2 pronuclear.

Baseline, hormonal, and cycle criteria between groups of antagonists (B and C)

As shown in [Table 2](#), there were no significant differences found between the studied groups among baseline, hormonal, and cycle criteria between group B and C (P>0.05)

Table 2. Differences between Group B and C among baseline, hormonal, and cycle criteria.

| Variables (Mean± SD) | Group B (mean ± SD) (n=34) | Group C (mean ± SD) (n=34) | P Value |
|-------------------------------|----------------------------|----------------------------|---------|
| Age | 31.9 ± 2.6 | 32.5± 3.8 | 0.4 |
| BMI | 28.4 ±3.8 | 28.0± 4.7 | 0.7 |
| Duration of infertility | 7.6±4.32 | 6.8±3.5 | 0.4 |
| LH (IU/L) | 4.06 ± 2.61 | 5.8 ± 0.9 | <0.001* |
| E2 (pg/ml) | 47.8±21.44 | 49.3±18.4 | 0.7 |
| GnRHa (IU) | 2408.0± 633.7 | 2456.1±689.2 | 0.76 |
| FSH (IU/L) | 5.9±1.6 | 6.4±1.9 | 0.2 |
| AFC | 14.8±5.7 | 15.6±3.4 | 0.4 |
| Duration of stimulation (day) | 9.7 ± 1.4 | 9.5 ± 1.1 | 0.5 |
| ET on hCG day | 9.9 ± 2.2 | 10.3 ± 2.1 | 0.4 |
| Follicular output rate | 0.89 ± 0.5 | 0.8±0.2 | 0.3 |
| Oocytes retrieved | 15.5 ± 7.7 | 14.8±7.1 | 0.6 |
| MII oocytes | 11.8 ± 6.3 | 11.6±5.9 | 0.8 |
| High quality embryos | 4.9 ± 2.3 | 4.5±2.4 | 0.4 |

| Variables (Mean± SD) | Group B (mean ± SD) (n=34) | Group C (mean ± SD) (n=34) | P Value |
|----------------------|----------------------------|----------------------------|---------|
| 2PN zygotes | 9.5 ± 6.1 | 9.4±5.7 | 0.9 |

*:P. value <0.05 (significant)

Table 3 and Figure 1, showed that a positive hCG test was found in 27 (79.4%) women in Group A while it was positive in 19 (55.9%) women in Group B with a significant difference (P=0.03), clinical pregnancy was found in 25 (73.5%) women in Group A while it was

positive in 17 (50.0%) women in Group B with a significant difference (P=0.04), and ongoing pregnancy was found in 24 (70.6%) women in Group A while it was positive in 15 (44.1%) women in Group B with a significant difference (P=0.01).

Table 3. Comparison of pregnancy outcomes in Group A and B

| Variables | Group A | | Group B | | P.value |
|---------------------------|---------|------|---------|------|---------|
| | (n=34) | % | (n=34) | % | |
| Positive hCG test | 27 | 79.4 | 19 | 55.9 | 0.03* |
| Clinical pregnancy, n (%) | 25 | 73.5 | 17 | 50.0 | 0.04 * |
| Ongoing pregnancy, n (%) | 24 | 70.6 | 15 | 44.1 | 0.01 * |

*:P. value <0.05 (significant)

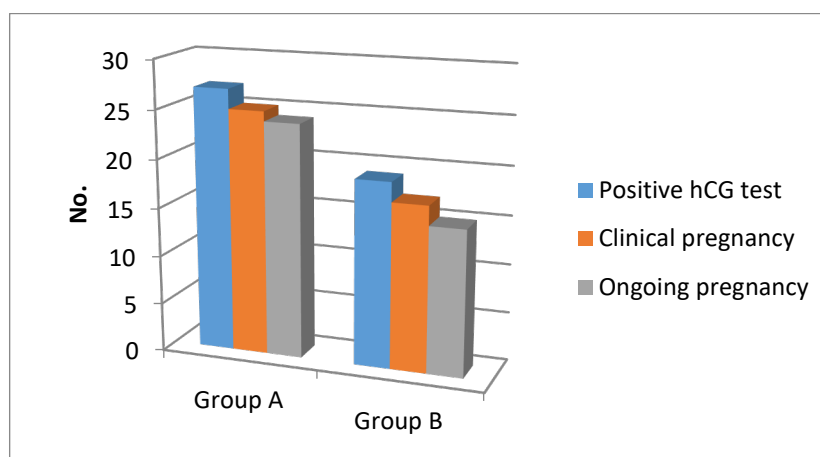


Figure 1. Differences between pregnancy outcomes between Group A and B.

Table 4, show that positive hCG test was found in 19 (55.9%) women in Group B while it was positive in 18 (52.9%) women in Group C with no significant difference (P=0.8), clinical pregnancy was found in 17 (50.0%) women in Group B while it was positive in 16

(47.1%) women in Group C with no significant difference (P=0.8), and ongoing pregnancy was found in 15 (44.1%) women in Group B while it was positive in 16 (47.1%) women in Group C with no significant difference (P=0.9).

Table 4. Comparison of pregnancy outcomes in Group B and C

| Variables | Group B | | Group C | | P.value |
|---------------------------|---------|------|---------|------|---------|
| | (n=34) | % | (n=34) | % | |
| Positive hCG test | 19 | 55.9 | 18 | 52.9 | 0.8 Ns |
| Clinical pregnancy, n (%) | 17 | 50.0 | 16 | 47.1 | 0.8Ns |
| Ongoing pregnancy, n (%) | 15 | 44.1 | 16 | 47.1 | 0.9 Ns |

P. value >0.05 (not significant)

Discussion

The GnRH antagonist protocol has proper data showing that it can prevent severe ovarian hyperstimulation syndrome in cases of polycystic ovary syndrome. GnRH antagonists are hormones that act through a competitive blocking system of GnRH receptors present on the surface of the anterior pituitary; in this way, the production of gonadotropins (FSH and LH) is directly blocked. Unlike agonists, they do not require a desensitization period; their action is immediate, and their half-life is very short. When acting under competitive inhibition of GnRH receptors, there is no activation. Therefore, the flare-up effect described with the use of agonists does not occur (14). It was approved that LH can be an indicator for the timing and dosage of antagonist administration in current research, which is in agreement with (10), which showed that a threshold of LH stimulation is needed for appropriate follicular development and oocyte maturation. High or low levels of LH can cause infertility. In the current prospective cross-sectional study, the clinical value of measurement of serum levels of LH was evaluated through controlled ovarian stimulation with follicular stimulating hormone monotherapy to regulate the requirement for addition of antagonists. Then we established that there is no difference in hormonal assay and embryo criteria among women with low levels of endogenous luteinizing hormone (<4 IU/L) in controlled ovarian stimulation.

Researchers revealed that GnRH antagonists have a direct effect on levels of endogenous luteinizing hormone (LH), which are related to oocyte development and controlled ovarian stimulation outcomes, (11) found that higher levels of LH in the follicular phase agreed that in the regular or stimulated cycles (17).

Conversely, Chen et al., concluded that low levels of luteinizing hormone are linked to increased early pregnancy loss in ART women (18). The use of antagonists that act as regulators of luteinizing hormone levels, hence the justification behind their use in a properly individualized stimulation regimen. This is due to the fact that the antagonists themselves regulate the level of luteinizing hormone.

The most important findings in the current study were the significantly higher positive hCG test, clinical pregnancy and going pregnancy in Group A (LH<4 IU/L) than in Group B (LH <4 IU/L). This agrees with a study by Liu M et al., 2019 that included 576 women stimulated by monotherapy recombinant rFSH in a GnRH protocol. They concluded that women with low levels of luteinizing hormone (<4 IU/L) do not need antagonist administration (7).

We proposed that a more significant suppression of luteinizing hormone levels could explain the small pregnancy results among women with low levels of luteinizing hormone (4 IU/L) who added the antagonist

as co-treatment. This was because these women received both treatments. Formerly, they found that low pregnancy rates were registered in women with low serum levels of luteinizing hormone or who presented with a severe decrease in levels of luteinizing hormone from normal levels. Moreover, other studies using minor OSC with antagonists found that the rate of pregnancy when the serum level of luteinizing hormone was at a lower concentration than 1/3rd of normal levels at the time of gonadotropin administration, both fertilization and implantation were markedly inferior (19).

Zhang et al., revealed that a relative decrease in mid-follicular luteinizing hormone concentrations throughout gonadotropin-releasing hormone agonist cycles leads to a decrease in the rate of live birth (20). The current report coincides with these explanations of lowered clinical and ongoing pregnancy rates, perhaps produced by variations in LH because of the addition of GnRH antagonists.

Depalo et al., approve the importance of luteinizing hormone levels for controlled ovarian stimulation outcomes (13). The luteinizing hormone profile significantly affected pregnancy outcomes; the ranks of the luteinizing hormone at the reference line and close to the end of stimulation were much lower in females who went on to become pregnant. Previous research has shown that variations in levels of luteinizing hormone throughout the follicular phase may be disadvantageous to endometrial receptivity and, as a consequence of the rate of pregnancy.

Conclusion

LH is a glycoprotein hormone discharged by the gonadotropin cells to stimulate the activity of the gonads of the anterior pituitary gland, which demonstrate its significant impact on hormone generation, ovulation promotion and luteinization. LH levels can indicate the time of antagonist addition. Cases with LH levels less than 4 IU/L during a period of controlled ovarian stimulation, may not need antagonist usage. We conclude that women with LH <4 IU presented a significantly higher pregnancy rate than those with ≥ 4 IU and did not need GnRH antagonist addition as co-treatment.

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Author's Contributions

Dr. May Kassim Khalaf proposed the main idea and collected data. Dr. Fadia J Alizzi conceptualized and designed the analysis and contributed data. Dr. Ammar

Mohammed Qassim performed the analysis and wrote the final version of the paper.

Conflict of Interest

The authors declare no conflict of interest.

Found or Financial Support

Not Applied.

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