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High basal LH levels are associated with improved cycle outcomes of assisted reproduction

Yüksek bazal LH seviyeleri daha iyi yardımcı üreme siklus sonuçları ile ilişkilidir

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Abstract

Aim: Several parameters are used to observe the ovarian responsiveness to gonadotropin stimulation. Basal LH levels have been suggested on ovarian response as well as basal FSH levels. This study was aimed to evaluate the correlation of basal LH levels with cycle and pregnancy outcomes in patients who underwent GnRH-antagonist IVF (in-vitro fertilization) cycles.

Methods: This retrospective cohort study recruited a total of 317 cycles with values of FSH <10 IU/L. Basal hormonal parameters (FSH, LH, estradiol) were recorded prior to ovarian stimulation. Patients were treated with GnRH antagonist protocols and stimulated with recombinant FSH. The patients were categorized according to designated threshold levels for LH values (Group 1: LH <4.1 IU/L and Group 2: LH ≥4.1). The number of total retrieved oocytes and mature oocytes, implantation rate, clinical pregnancy rate and ongoing pregnancy rate were analyzed between study groups.

Results: Group 2 had a higher number of retrieved oocytes and mature oocytes compared to Group 1 (P=0.006 and P=0.03, respectively). Although not statistically significant, there was a trend towards higher rates of pregnancy on high LH levels. Clinical and ongoing pregnancy rates were insignificantly lower in Group 1 (38.3% vs. 48.5%, P=0.162 and 29.4% vs. 34.0%, P=0.535; respectively). The basal LH levels positively correlated with the number of oocytes, and the combination with low FSH levels was also found to be associated with higher number of retrieved oocytes and peak estradiol levels.

Conclusions: Elevated basal LH levels provide a beneficial effect on cycle outcome such as number of retrieved oocytes. However, clinical pregnancy rates were found to be similar between below and above the threshold of LH levels.

Keywords: Luteinizing hormone, IVF (in-vitro fertilization), Infertility, Oocyte number, Pregnancy rate

Öz

Amaç: Gonadotropin stimülasyonuna over yanıtını değerlendirmek için birçok parametre bulunmaktadır. Basal LH seviyeleri FSH seviyelerine ek olarak over yanıtında önerilmektedir. Bu çalışma ile GnRH-antagonist IVF (in-vitro fertilizasyon) siklusu uygulanan hastalarda bazal LH seviyelerinin siklus ve gebelik sonuçları ile ilişkisini değerlendirmek amaçlanmıştır.

Yöntemler: Retrospektif kohort çalışmaya FSH değeri 10 IU/L'den daha düşük olan 317 siklus dahil edilmiştir. Bazal hormonal bulgular (FSH, LH, estradiol) ovaryan stimülasyon başlamadan önce kaydedildi. Hastalara GnRH-antagonist protokol ve rekombinant FSH tedavisi uygulandı. Hastalar; LH değeri için belirlenmiş olan eşik değerlere göre kategorize edilmişlerdir (Grup 1: LH <4,1 IU/L ve Grup 2: LH ≥4,1). Elde edilen toplam oosit sayısı, matür oosit sayısı, implantasyon oranı, klinik gebelik ve devam eden gebelik oranı çalışma grupları arasında analiz edilerek karşılaştırıldı.

Bulgular: Grup 2 hastalarda, Grup 1 ile karşılaştırıldığında daha fazla oosit sayısı ve matür oosit sayısı tespit edilmiştir (P=0,006 ve P=0,03). İstatistiksel olarak anlamlı olmasa dahi, yüksek LH seviyelerinde daha yüksek gebelik oranları lehine bir eğilim saptandı. Klinik gebelik ve devam eden gebelik oranları Grup 1'de daha düşüktü ancak bu farklılık istatistiksel olarak anlamlı değildi (Klinik ve devam eden gebelik için sırasıyla %38,3'e karşı %48,5, P=0,162 ve %29,4'e karşı %34,0, P=0,535). Bazal LH seviyeleri oosit sayısı ile pozitif olarak korele olarak saptandı ve düşük FSH seviyeleri ile kombinasyonu da daha fazla oosit sayısı ve pik östrojen düzeyleri ile ilişkili bulundu.

Sonuç: Artmış bazal LH seviyeleri toplam elde edilen oosit sayısı gibi siklus sonuçları üzerinde faydalı etki sağlayabilir. Bununla birlikte klinik gebelik oranları LH seviyesi eşik değerinin altında ve üstünde olanlar arasında benzer olarak tespit edildi.

Anahtar kelimeler: Luteinize edici hormon, IVF (in-vitro fertilizasyon), İnfertilite, Oosit sayısı, Gebelik oranı

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Introduction

Optimal ovarian responsiveness and normal follicular growth are essential especially in assisted reproductive techniques (ART). The main aim of ovarian stimulation is to provide a higher number of mature oocytes for in-vitro fertilization (IVF) cycles which results in obtaining high-quality embryos [1]. Several parameters have been reported to predict the response of ovarian stimulation. Age is the most important variable that affects fertility potential. The baseline predictors of ovarian response are female's age, day-3 FSH (follicle-stimulating hormone), LH (luteinizing hormone), estradiol, and anti-Mullerian hormone (AMH) [2-5]. The most commonly used marker is day-3 FSH level and it may reflect the ovarian reserve concerning female age [2,6,7]. Baseline LH levels are also used to assess infertile women prior to ART cycles [8]. Normal follicular growth and maturation require the contribution of both FSH and LH stimulation according to the two-cell theory, however the main role had been attributed to FSH value until now [9]. Endogenous LH activity is necessary to get optimal development of follicles, while low LH levels may be an indicator of poor activity for the hypothalamus-pituitary-ovarian axis [10]. LH levels may have an impact on ovarian response especially on normal FSH levels [10,11]. Several studies evaluated the efficacy of LH to predict the response to ovarian stimulation and the association between LH levels and treatment outcomes [11-14], but the results are still controversial about the precise role of LH. The purpose of this study was to determine the relationship between baseline LH levels and ovarian response and treatment outcomes in ART cycles. The primary outcomes were correlation of LH levels with the total dose of gonadotropins used and the number of retrieved oocytes. The secondary outcome was to evaluate pregnancy outcomes.

Materials and methods

This retrospective cohort study was carried out at a reproductive endocrinology and infertility unit of a university-based hospital between 2017 and 2019. The study was approved by the local Ethics Committee of Eskisehir Osmangazi University Faculty of Medicine and conducted in accordance with the principles of Helsinki Declaration (2020/ Ref. No: E.7215-2020/43). All the patients who underwent IVF/ICSI cycles were evaluated. Inclusion criteria were age <45 years at the cycle initiation, and basal FSH <10 IU/L. Patients who underwent fresh embryo transfer cycles were included in the study population. A total of 978 cycles were evaluated and cycles with characteristics including basal FSH≥10 IU/L, endocrine abnormalities such as thyroid disorders and hyperprolactinemia, high ovarian response such as polycystic ovarian syndrome, long agonist protocols and frozen-thaw embryo transfers were excluded from the study. In this regard, we excluded low and high response cycles, and selected homogeneous group to assess only the normoresponders.

Demographic characteristics and basal (cycle day-2 or 3) parameters were evaluated. Basal hormone levels such as FSH (follicle-stimulating hormone), LH (luteinizing hormone), estradiol, AMH (anti-Mullerian hormone), were determined on day-2 or 3 of the menstrual cycle prior to ovarian stimulation. The patient's serum samples were measured for FSH, LH by electrochemiluminescent immunometric assay using commercial kits. We analyzed the data and determined the cut-off values for FSH and LH levels to discriminate the successful and unsuccessful pregnancy outcome. The cut-off levels for FSH and LH levels were determined as 6.2 and 4.1, respectively. According to the cut-off level for LH levels, the study population was divided into two groups as below and above the threshold levels. We compared the outcomes between the study groups.

All patients underwent GnRH-antagonist protocol for ovarian stimulation with a daily injection of recombinant FSH (Gonal-f, Merck, Germany) starting on cycle day-2 or 3. The doses of gonadotropins were customized according to the patient's age, BMI and basal antral follicle count. GnRH antagonist (Cetrorelix, Merck, Germany) was administered depending on the size of the leading follicle as 14 mm or serum estradiol level exceeding 300 pg/mL and continued until the hCG administration. Triggering of ovulation was achieved with recombinant hCG (Ovitrelle 250 μg; Merck, Germany) when at least three follicles reached 18 mm in diameter. Transvaginal-guided oocyte retrieval was carried out 36 hours after triggering. The retrieved oocytes were fertilized by standard IVF or ICSI procedure. Embryo development was observed and embryo quality was determined according to guidelines [15,16]. Embryo transfers were performed under ultrasound guidance after assessing the embryo quality on day-3 (cleavage stage) or day-5 (blastocyst stage) of the fertilization. Cycle outcomes such as stimulation parameters (dose of gonadotropins, number of follicles), number of oocytes and fertilization rate were also recorded. Vaginal progesterone gel (Crinone 8% gel, Merck, Germany) was administered as a luteal phase support until the 9th of gestational week.

Serum beta-hCG levels were measured to determine the cycle outcome as the implantation rate, 12 days after embryo transfer. Clinical pregnancy was defined as the presence of a gestational sac and fetal heartbeat after 6-7 weeks of gestation. Ongoing pregnancy was defined as pregnancies that reached 25 weeks gestation or more.

Statistical analysis

Statistical evaluation was performed with the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL). Descriptive parameters and cycle outcomes were reported as mean standard deviation and median values according to the distribution of the data. Normal or abnormal distribution was determined using the Kolmogorov-Smirnov test. The Student's t-test was used to compare normally distributed data. In cases of non-parametric continuous and categorical data, the differences were observed with Mann-Whitney U and Kruskal-Wallis tests. The Pearson chi-square test or Fisher Exact test was carried out to analyze categorical data. Spearman correlation analysis was performed to establish the correlation between basal LH levels and cycle outcomes. We performed the receiver operating characteristics (ROC) curve analysis to determine the most efficient threshold values for serum LH and FSH levels to discriminate between successful and unsuccessful cycle outcomes. A *P*-value of <0.05 was considered statistically significant.

Results

A total of 978 IVF/ICSI cycles were evaluated for the study population. We included the GnRH antagonist protocol and fresh embryo transfer cycles in patients with FSH<10 IU/L. Six hundred and sixty-one cycles which did not meet the inclusion criteria were excluded from the study. Eventually, the present study included 317 cycles to analyze. The mean age was 31.9(4.6) years, basal FSH and LH levels were 6.9 (1.5) IU/L and 6.4 (3.0) IU/L for overall study population, respectively. The implantation, clinical pregnancy and ongoing pregnancy rates were reported as 55.9%, 46.4% and 33.1%, respectively. We determined a cut-off value for LH levels as 4.1 to distinguish the highest and lowest pregnancy rates. Patients in Group 1 with basal LH <4.1 IU/L reported 64 women, while Group 2 of patients with basal LH ≥4.1 IU/L reported 253 women. There were no differences between the study groups with regards to mean age and the duration of infertility. Table 1 shows baseline demographic and hormonal characteristics. The antral follicle count on the day-2 or 3 was slightly higher in Group 2. The basal LH and AMH levels were also significantly higher in the high LH group (P<0.001 and P=0.027, respectively). The ovarian stimulation results and cycle outcomes of the groups are shown in Table 2. We did not find any significant differences between the study groups for the starting dose of gonadotropins, duration of infertility and the total dose of gonadotropins. The mean total dose of gonadotropins was found lower in favor of Group 2 compared to Group 1, but did not reach significance (1930.1 IU vs. 2031.8 IU, P=0.157; respectively). Although the total dose of gonadotropins was lower in Group 2, the peak estradiol levels on the day of hCG were found to be significantly higher in Group 2 compared to Group 1 (P=0.001). Moreover, we observed that the total number of retrieved oocytes and mature oocytes were also significantly higher in the group with LH ≥4.1 IU/L (Table 2). We also analyzed the correlation of LH levels with the cycle outcomes. A significantly positive correlation was present between LH levels and cycle outcomes such as the number of retrieved oocytes and mature oocytes (Figure 1). We also found a negative correlation with LH levels for the total dose of gonadotropins, which means that the dose of gonadotropins decreases with increase in LH levels (Figure 1). FSH value is as important as LH levels to achieve effective IVF outcomes. However, we have also identified a cut-off value for FSH values as 6.2 IU/L and we think that the higher levels may indicate poorer outcomes. Therefore, we categorized patients into four groups with these cut-off values for both FSH and LH levels as Low LH-Low FSH, Low LH-High FSH, High LH-Low FSH and High LH-High FSH. Figure 2 shows the cycle outcomes in terms of FSH and LH categorization. The results were found to have significantly improved in the 'High LH-Low FSH' group of patients (Figure 2) (P<0.001). Although there was a trend toward a higher rate of implantation, clinical pregnancy, and ongoing pregnancy rates in the high LH group, we did not find any significant differences between Groups 1 and 2 regarding the pregnancy outcomes (Table 3).

Table 1: Demographic and basal parameters of the patients

	Group 1 (LH <4.1) (n=64)	Group 2 (LH ≥4.1) (n=253)	*P*-value
Age (years)	31.2 (4.3)	32.1 (4.7)	0.165
BMI (kg/m^2)	27.3 (5.7)	24.7 (4.7)	0.001
Duration of infertility (years)	5.3 (3.6)	5.2 (3.8)	0.501
Baseline AFC	10.4 (5.2)	11.9 (5.5)	0.027
Baseline FSH (IU/L)	6.2 (1.8)	7.1 (1.4)	0.001
Baseline LH (IU/L)	3.4 (0.7)	7.2 (2.8)	<0.001
Baseline FSH/LH ratio	1.9 (0.6)	1.1 (0.4)	<0.001
AMH (U/L)	2.2 (1.8)	3.2 (2.5)	0.001

Values are defined as Mean (SD), LH: luteinizing hormone, BMI: body mass index, AFC: antral follicle count, FSH: follicle-stimulating hormone, AMH: anti-Mullerian hormone

Table 2: The ovarian stimulation and cycle outcomes

	Group 1 (LH <4.1) (n=64)	Group 2 (LH ≥4.1) (n=253)	*P*-value
Starting dose of gonadotropins (IU)	230.7 (56.1)	218.1 (54.4)	0.069
Antagonist starting day	7.0 (0.9)	7.2 (1.1)	0.658
Duration of stimulation (days)	8.9 (1.3)	8.8 (1.5)	0.477
Total dose of gonadotropins (IU)	2031.8 (624.5)	1930.1 (642.1)	0.157
Serum P on the day of hCG (ng/mL)	0.66 (0.38)	0.74 (0.44)	0.217
Serum estradiol on the day of hCG (pg/mL)	1680.9 (1160.5)	2025.4 (1030.9)	0.001
Endometrial thickness on the day of hCG (mm)	9.1 (1.6)	9.3 (1.5)	0.067
Total follicle number >15 mm	4.8 (2.6)	5.1 (2.6)	0.379
Number of total retrieved oocytes	7.1 (3.7)	8.5 (3.8)	0.006
Number of Total mature oocytes	4.8 (2.7)	5.8 (3.3)	0.030
Fertilization rate (%)	92.4 (18.1)	94.2 (14.9)	0.686

Values are defined as Mean (SD), LH: luteinizing hormone, P: progesterone, hCG: human chorionic gonadotropin

Table 3: The pregnancy outcomes

	Groups 1 (LH <4.1) (n=64)	Group 2 (LH ≥4.1) (n=253)	*P*-value
Implantation rate (%)	46.7	58.2	0.108
Clinical Pregnancy rate (%)	38.3	48.5	0.162
Ongoing pregnancy rate (%)	29.4	34.0	0.535

LH: luteinizing hormone

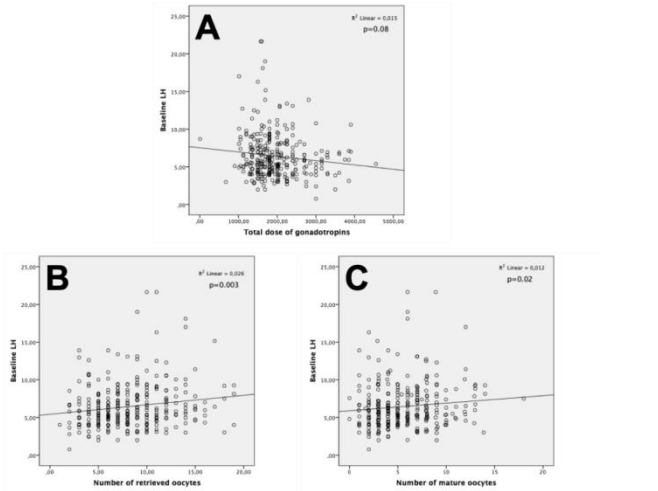

Figure 1: The correlation analysis of basal LH levels with; A: Total dose of gonadotropins B: The number of retrieved oocytes C: The number of mature oocytes

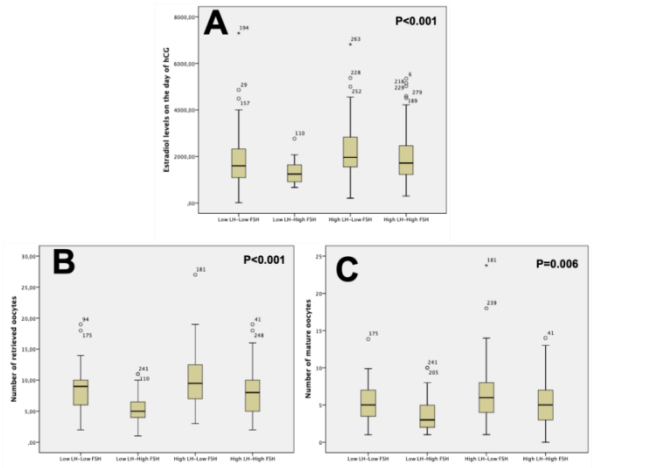

Figure 2: The combination analysis of basal FSH and LH levels according to the cut-off levels A: Estradiol on the day of hCG B: The number of retrieved oocytes C: The number of mature oocytes

Discussion

In this study, we investigated the effect of basal LH levels on IVF cycle outcomes and the correlation between LH levels and the number of retrieved oocytes. We established that higher LH values positively correlated with the number of retrieved oocytes and mature oocytes, although there were no significant differences regarding the pregnancy results. We also observed a trend toward the higher pregnancy outcomes in patients with higher LH values, but no statistical differences. The basal FSH and LH levels were also found to be associated with the cycle outcomes in ART cycles, however optimal combination for successful outcomes such as peak estradiol levels and the number of retrieved oocytes was found to be low FSH and high LH levels in patients with FSH <10 IU/L.

Mukherjee et al. [11] suggested that low LH levels (<3 IU/L) were predictive in determining poor response to ovarian stimulation. Several studies investigated whether high LH levels had a positive impact on ART outcome [17-20]. Barroso et al. [12] demonstrated that a higher number of retrieved oocytes was obtained in patients with high LH values, with a borderline significance. In an observational study, LH levels were divided into three groups and the number of oocytes was found to be significantly higher in the LH ≥8 IU/L group [17]. The authors did not find any significance regarding clinical pregnancy and live birth rates between the different basal LH levels. A prospective observational study suggested that the significantly higher number of oocytes was retrieved in the LH >3 IU/L group of patients than in the LH ≤3 IU/L group [18]. They showed similar total gonadotropin doses used for ovarian stimulation among study groups. There were higher pregnancy rates in favor of the high LH subgroup, although there were no significant differences between the high and low LH subgroups (30.6% vs. 18.5%, P=0.17). In a recent retrospective data analysis, Sun et al. [20] observed that the number of retrieved oocytes, mature oocytes were significantly greater in the group with LH ≥10 IU/L than in the groups with LH <10 IU/L. The total dose of gonadotropins and duration of stimulation were also lower in the high LH subgroup than the low LH cases. They also demonstrated that more total embryos, more top quality embryos and high peak estradiol levels were significantly in the group with basal LH ≥10 IU/L than the group with lower LH levels. However, these improved results did not have an effect on pregnancy outcomes. Similar to current literature, we also found that the number of oocytes and peak estradiol levels were significantly higher in the high LH group. The pregnancy rates did not differ significantly between the high and low LH groups, although there was a trend toward higher LH levels. It has been speculated that LH may have an influence on cytoplasmic maturation and embryo quality and may lead to an improvement in the implantation potential [21,22]. However, the effect of basal LH on fertility potential is still controversial. Some investigators established that high exposure to LH may have a deleterious effect on ART cycles especially in polycystic ovarian syndrome and it may cause early pregnancy loss [23].

Noci et al. [10] suggested that intra-ovarian regulators may be decreased with LH levels below 3 IU/L and the responsiveness to gonadotropins is reduced due to low LH levels. In a retrospective study, Tas et al. [24] evaluated the effect of myo-inositol on ovarian stimulation and the LH levels were found to be higher in the study group. They did not find any significant improvement in the study group in terms of ovarian response. It was suggested that the low basal LH levels may be associated with reduced ovarian responsiveness to ovarian stimulation in ART cycles [10,11,25]. Noci et al. [26] suggested that some women presenting low LH levels had some impairment of follicular growth and differentiation in GnRH analog suppressed cycles and the higher dose of gonadotropins might overcome these undesirable results. In GnRH analog suppressed cycles, the ovarian response to FSH is regulated independently of basal serum LH levels [26-28]. The low LH levels were not the only factor that was associated with a negative impact on IVF cycle outcome, although there was also a higher ovarian response to FSH stimulation in favor of high LH levels for cycles with a combination of GnRH-agonist and pure FSH [12]. We found >15 mm similar follicle numbers on the day of hCG administration between groups. Moreover, the total number of retrieved oocytes and mature oocytes were significantly higher above the LH threshold. We demonstrated that the total dose of gonadotropin used was higher in patients with low LH levels but this difference did not attain any significance. Similar to the recent studies, we observed that patients having low basal LH levels had a lower response to ovarian stimulation and a lower number of oocytes in ART cycles.

We used only recombinant FSH for ovarian stimulation in the GnRH-antagonist cycles, however there were controversial results about using hMG (human menopausal gonadotropin) or only FSH for ovarian stimulation in GnRH-agonist IVF/ICSI cycles [29]. Theoretically, the addition of LH may be beneficial in cases with low LH levels. The requirement of LH may have a threshold during folliculogenesis, and it may affect follicle growth and oocyte quality. On the contrary, Kolibianakis et al. [30] demonstrated that the addition of recombinant LH did not increase live birth rates in patients treated with GnRH analogs and FSH for IVF cycles. In a large retrospective study, Lyu et al. [19] also concluded that the supplementation of recombinant LH did not improve cycle outcome in the GnRH antagonist cycles. Most of the studies were performed especially in GnRH analogue suppressed cycles with ovarian stimulation. Lyu et al. [19] included both GnRH agonist and antagonist cycles to the study population similar to our study. They demonstrated that the pregnancy rates were not significantly different between FSH/LH ratio above and below the threshold in patients with FSH<10 IU/L, although these rates were different within GnRH antagonist cycles between study groups.

The effect of basal LH levels may be put forward with the ratio of FSH/LH like in the study of Lyu et al. [19]. It was speculated that a high FSH/LH ratio may lead to low ovarian responsiveness, low oocyte quality and low embryo quality [12]. Prasad et al. [18] evaluated the basal LH level and FSH/LH ratio for predicting IVF cycle outcomes. The number of oocytes and pregnancy rates were found to be significantly higher in the FSH/LH <2 group compared to FSH/LH ≥2. It was demonstrated that the FSH/LH ratio increased based on lower LH levels, and was not associated with FSH levels [12,14]. A retrospective

study also established that the total number of oocytes, mature oocytes, number of top quality embryos were significantly higher in the FSH/LH <2 group than the FSH/LH ≥2 group [19]. Ho et al. [1] also observed that increased FHS/LH ratio was related to the lower number of retrieved oocytes and lower peak estradiol levels. The elevated FSH/LH ratio was shown as a predictor for poor ovarian response in patients with normal FSH levels [11,12]. On the other hand, some authors suggested using individual FSH, LH levels and combinations instead of using ratios, to estimate the ovarian response to the gonadotropin stimulation [31]. Brodin et al. [31] reported a significantly higher number of oocytes, higher pregnancy rates and lower doses of FSH in the high LH and low FSH combinations according to the thresholds of their study in the GnRH-agonist IVF cycles. We also demonstrated a higher number of oocytes and lower doses of gonadotropins in the high LH and low FSH combinations, but did not find any significant differences regarding pregnancy rates. We also suggested that the pregnancy rates may have been affected not only by hormonal values but also by multi-factorial parameters, consequently it is more adequate to evaluate the association of hormonal levels with ovarian stimulation results. Bansal et al. [32] also found similar cycle outcomes, however they showed the lowest dose of gonadotropins in the lower levels of both FSH and LH group.

Limitations

The present study has some limitations. The most important limitation of our study is its retrospective nature. On the other hand, the strengths of our study were that the study consisted of a study population with homogeneous patients who were normoresponders and performing only GnRH-antagonist protocol to determine the efficacy of basal LH levels. Additional large prospective studies are required to confirm our findings.

Conclusion

We established that higher basal LH levels were associated with improved cycle outcomes. However, it was not a useful parameter for predicting successful pregnancies. The cut-off values of FSH and LH levels may vary according to local laboratory variations, so each center should determine their own threshold for these values. The unexpected low ovarian response may be encountered especially in young patients with normal FSH levels. In these patients, basal LH levels may be beneficial to determine appropriate ovarian stimulation dose and protocol.

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