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PROGESTERONE IN LATE FOLLICULAR PHASE AND PREGNANCY RATES

Progesterone change in the late follicular phase affects pregnancy rates both agonist and antagonist protocols in normoresponders: a case-controlled study in ICSI cyclesBerfu Demir¹, Inci Kahyaoglu¹, Altay Guvenir², Neslihan Yerebasmaz¹, Sadiman Altinbas¹, Berna Dilbaz¹, Serdar Dilbaz¹, and Leyla Mollamahmutoglu¹¹Department of Obstetrics and Gynecology, Etlik Zubeyde Hanim Women's Health Teaching and Research Hospital, Ankara, Turkey and²Department of Computer Engineering, Bilkent University, Ankara, Turkey**Abstract**

Objective: The aim of the presented study is to investigate the impact of progesterone change in the late follicular phase on the pregnancy rates of both agonist and antagonist protocols in normoresponders.

Study design: A total of 201 normoresponder patients, who underwent embryo transfer were consecutively selected. 118 patients were stimulated using a long luteal GnRH agonist protocol and 83 using a flexible antagonist protocol. The level of change in late follicular phase progesterone was calculated according to the progesterone levels on the hCG day and pre-hCG day (1 or 2 days prior to hCG day) measurement.

Results: Clinical pregnancy rates were comparable between long luteal and antagonist group (35.6 and 41%, respectively). The incidence of progesterone elevation on the hCG day was 11% in long luteal and 18% in antagonist group ($p=0.16$). In pregnant cycles, p levels both on the hCG day and pre-hCG day measurement were significantly higher in antagonist than agonist cycles ($p=0.029$, $p=0.038$, respectively). The change of p level was statistically significant in non-pregnant cycles both for the agonist (-0.17 ± 0.07 ; 95% CI: -0.29 to -0.37) and antagonist groups (-0.18 ± 0.07 ; 95% CI: -0.31 to -0.04).

Conclusions: Late follicular phase progesterone levels were stable during the cycles of pregnant patients irrespective of the protocols and were shown to be higher in pregnant patients in antagonist cycles when compared to agonist cycles.

KeywordsGnRH agonist, GnRH antagonist, intracytoplasmic sperm injection, *in-vitro* fertilization, progesterone**History**

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Introduction

The incidence of premature LH surge is significantly reduced using GnRH analogs in *in vitro* fertilization (IVF) cycles [1]. Premature progesterone rise is a different entity, which can have significant effects on *in-vitro* fertilization outcomes. Literature about this topic demonstrates a wide range of incidences, varying from 2 to 35% [2,3].

Progesterone rise has recently been associated with the number of preovulatory follicles, which is excessive in number but each produces a normal amount of progesterone for the late follicular phase [4] and high E2 exposure [5,6]. Although late follicular phase progesterone rise is often seen in women displaying a good response to ovarian stimulation, it can also take place in poor

responders, hence through a different mechanism. These patients need longer stimulation and thus a significantly higher total FSH dose [7,8]. They may have an increased sensitivity to LH as another mechanism [9].

Whatever the mechanism of progesterone increase in the late follicular phase, progesterone exerts its detrimental effects through its action on the endometrium [3,10,11]. High serum progesterone levels on the day of HCG administration induce both advanced endometrial histological maturation [12] and differential endometrial gene expression [13,14], which may lead to implantation failure [2]. However, a single measurement during the whole cycle has limited value and statistical evaluation of multiple measurements throughout the cycle is a difficult issue.

Late follicular phase progesterone rise is an indicator of granulosa cell function in normoresponder patients. The aim of this study was to determine the effect of the change in late follicular phase serum progesterone levels on cycle outcomes of IVF/ET cycles in normoresponder patients undergoing either GnRH agonist or antagonist cycles.

Methods

The present case control study was conducted in the IVF clinic of Etlik Zubeyde Hanim Women's Health Teaching and Research Hospital, Ankara, Turkey, between January 2012 and June 2014.

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The inclusion criteria were as follows: (1) age <35; (2) basal FSH <14 IU/ml; (3) body mass index (BMI), 18–25 kg/m²; (4) antral follicle count >7; (5) previous IVF cycles <3; (6) ejaculated sperm used for the ICSI procedure; (7) all patients who underwent embryo transfer were selected consecutively. The study was approved by the Institutional Review Board (20.12.2012/number 160-2). Written informed consent was obtained from all subjects before their enrollment in the study.

Statistics of our clinic for the year 2014 showed that the distribution rates of stimulation protocols used in normoresponder patients was comparable (52 versus 48% for antagonists and agonists, respectively). The GnRH-agonist long protocol was begun in the mid-luteal phase of the previous cycle with leuprolide acetate (Lucrin, Abbot, Turkey). After onset of menstrual bleeding, when satisfactory pituitary desensitization was achieved (serum E2 level <50 pg/ml, endometrial thickness <5 mm, serum LH levels <5 IU/ml), the GnRH agonist dose was reduced to half and gonadotrophin administration was started with daily use of recombinant FSH (Gonal-F; Merck Serono, Istanbul, Turkey or Puregon, Organon, Istanbul, Turkey). Dose of gonadotrophins was individualized according to the patient's age, baseline serum FSH concentration on day 3 and body mass index (BMI). In the GnRH-antagonist protocol, gonadotrophins were administered from day 2 of the cycle and co-treatment with a GnRH antagonist, 0.25 mg ganirelix (MSD Organon, Oss, The Netherlands) or 0.25 mg cetrorelix (Merck-Serono, Geneva, Switzerland), was begun when the diameter of the follicle reached 12 mm or the E2 level was 250 pg/ml.

Cycles were monitored by means of serial transvaginal ultrasound evaluation scans and serum determination of estradiol, progesterone and LH. The level of change in late follicular phase progesterone was calculated according to the progesterone levels on the hCG day and pre-hCG day measurement. The pre-measurement was conducted 1 or 2 days prior to hCG day. The non-significant change in the late follicular phase progesterone was accepted as stable change. The threshold level for progesterone elevation was accepted as $p > 2$ ng/ml.

For both study groups, final oocyte maturation was induced with the administration of rec-hCG (Ovitrelle; Merck-Serono, Istanbul, Turkey) (250 µg when BMI <29 kg/m² and 500 µg when BMI >29 kg/m²) when at least three follicles of 17 mm were present. Oocyte retrieval (OPU) was performed 35.5–36 h after the administration of the rec-hCG preparation by transvaginal ultrasound-guided aspiration.

The embryo evaluation and scoring was performed by using appropriate scoring systems modified from previously described systems [15,16]. Day 2 embryos were classified according to size, nucleation and cytoplasmic morphology of blastomeres (percentage of anucleate fragments; cleavage speed and zona pellucida thickness) 42–44 h after the insemination. On Day 3, embryos were scored 64–65 h after insemination for cell number and degree of fragmentation and cell size. Blastocyst stage embryo scoring was performed based on the number of even-sized cells, visible inner cell mass and continuous trophoctoderm with sufficient cells. Embryos were classified from Grades 1 to 5 (best to worst).

Luteal support was given by either vaginal progesterone (Crinone 8% gel, Serono, Istanbul) twice a day or vaginal progesterone plus 100 mg intramuscular progesterone from embryo transfer to pregnancy test. Pregnancy was determined by β-hCG levels in blood tests performed 12 days after embryo

transfer and clinical pregnancy was defined as the presence of a gestational sac with accompanying fetal heartbeat.

Hormonal immunoassays

Serum samples were analyzed using Immulite 2000 reproductive hormone assays (Diagnostic Product Corporation, Siemens, Los Angeles, CA). The sensitivity was 0.1 mIU/ml for FSH; 0.05 mIU/ml for LH; 15 pg/ml for E2 and 0.1 ng/ml for P. Intra-assay and inter-assay coefficients of variation were <3.6% and <4.3% for FSH; <4.8% and <10.7% for LH; <6.7% and <9.7% for E2 and <9.7% and <12.2% for P, respectively.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) Windows version 17.0 (SPSS Inc., Chicago, IL). Distribution of the continuous variables was checked using the Kolmogorov-Smirnov test. Student's *t*-test was used for variables with normal distribution. After testing the skewed distribution, comparisons between the groups were tested using the Mann-Whitney U-test. The chi-square test was used to analyze nominal variables. Continuous variables were expressed as mean ± standard error (SE). The level of change in late follicular phase progesterone was tested using paired samples *t*-test or two-related samples test according to the variables distribution. A value of $p < 0.05$ was accepted as statistically significant.

Results

A total of 201 patients, 118 patients undergoing a long luteal GnRH agonist protocol and 83 undergoing a flexible antagonist protocol were enrolled in the study. The demographic characteristics, progesterone levels and pregnancy rates of the groups are presented in Table 1. Demographic characteristics were comparable between the two groups (Table 1). Progesterone levels during the stimulation cycle of the pregnant and non-pregnant patients in antagonist and agonist cycles are shown in Figure 1.

Clinical pregnancy rates were 35.6% in the long luteal group and 41% in the antagonist group ($p = 0.44$). The incidence of progesterone elevation in late follicular phase (>2 ng/ml) was 11% in the long luteal group and 18% in the antagonist group ($p = 0.16$). There were no significant differences on the clinical pregnancy rates according to the day of embryo transfer in patients with and without embryo transfer (Table 2).

In pregnant cycles, P levels both on hCG day and pre-hCG day measurement were significantly higher in antagonist cycles than agonist cycles ($p = 0.029$ and $p = 0.038$, respectively) (Table 1). When the level of changes of P between the hCG day and pre-hCG day measurement was compared, no significant difference was found in pregnant cycles for both the agonist and antagonist groups. The change in P level was statistically significant in non-pregnant cycles in both the agonist (-0.17 ± 0.07 ; $p: 0.013$ CI 95%: -0.29 to -0.37) and antagonist groups (-0.18 ± 0.07 ; $p: 0.011$, CI 95%: -0.31 to -0.04) (Figure 1).

The comparison of pregnant and non-pregnant patients treated with the antagonist protocol revealed that only the number of good quality embryos was significantly higher in pregnant cycles ($p = 0.007$). Progesterone levels on the hCG day and pre-hCG day measurement were similar in pregnant and non-pregnant cycles (Table 3).

Table 1. Demographic features of the patients.

	Long luteal (n=118)	Antagonist (n=83)	p Value	95% CI
Age (years)	28.2 ± 0.4	28.4 ± 0.4	0.72	-1.27 to 0.90
BMI (kg/m ²)	24.6 ± 0.3	23.5 ± 0.4	0.019*	0.17 to 2.03
Number of previous cycles	1.5 ± 0.8	1.7 ± 0.1	0.79	-0.48 to 0.015
Baseline FSH (IU/ml)	7.1 ± 0.2	7.5 ± 0.2	0.31	-0.99 to 0.13
Baseline LH (IU/ml)	5.2 ± 0.2	5.8 ± 0.4	0.33	-1.448 to 0.21
Baseline E2 (pg/ml)	43.9 ± 2.1	44.2 ± 3	0.71	-7.337 to 6.82
Duration of infertility (months)	66.7 ± 3.8	69.9 ± 5	0.61	-15.38 to 9.017
AFC	15.8 ± 0.5	16 ± 0.7	0.84	-1.908 to 1.538
TPSC (million)	31.931 ± 5880	27.081 ± 5909	0.81	-12 033.7 to 21 734.0
Number of top quality embryos	2.2 ± 0.2	2.5 ± 0.2	0.29	
Rate of embryo cryopreservation	18.6	19.3	0.91	
Number of embryos transferred	1 (1-2)	1 (1-2)	0.64	
The day of embryo transfer (n, %)				
Day 3	43 (36.4)	34 (41)	0.52	
Day 5	75 (63.6)	49 (59)		
Clinical pregnancy rate	35.6%	41%	0.44	
Progesterone elevation rate (>2.0 ng/ml) (n, %)	13 (11%)	15 (18.1%)	0.16	
Progesterone levels in pregnant patients (ng/ml)				
hCG day pre-measurement	1.11 ± 0.1	1.37 ± 0.1	0.038*	-0.5 to 0.01
hCG day	1.24 ± 0.1	1.51 ± 0.1	0.029*	-0.51 to 0.027
Progesterone levels in nonpregnant patients (ng/ml)				
hCG day pre-measurement	1.19 ± 0.1	1.2 ± 0.1	0.67	
hCG day	1.37 ± 0.1	1.38 ± 0.1	0.87	

BMI, body mass index; FSH, follicle stimulating hormone; LH, luteinizing hormone; E2, estradiol; AFC, antral follicle count; TPMSC, total progressive motile sperm count; P, progesterone.

*Statistically significant, data were presented as mean ± SE and n (%), n (%), median (minimum & unknown_hyphen; maximum).

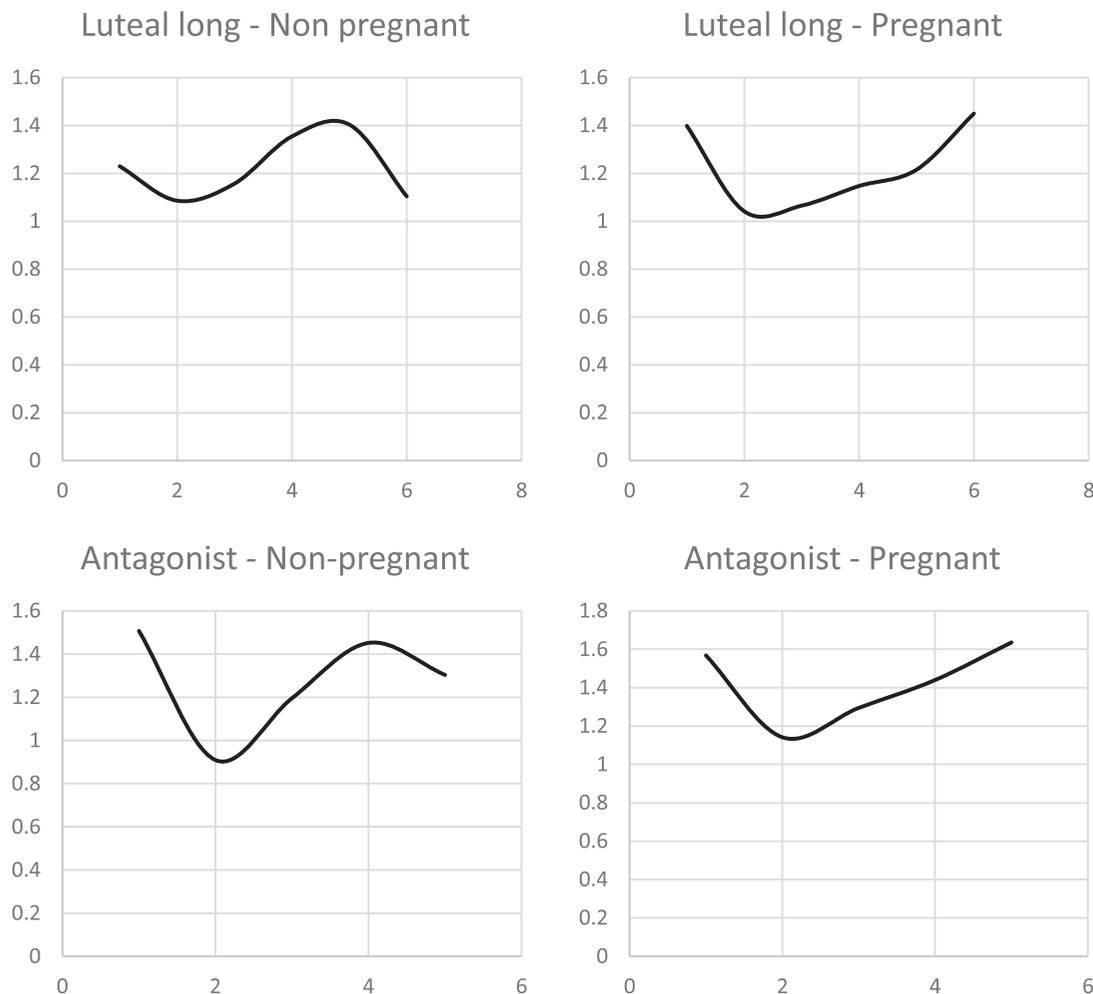


Figure 1. Means progesterone levels of pregnant and non-pregnant normo-responder patients in antagonist and long luteal cycles. *X axis: Progesterone measurement step through the stimulation period (2nd, 4th, 6th), y axis: Mean progesterone level (ng/ml).

In agonist cycles, the number of top-quality embryos and fertilization rates were found to be significantly higher in pregnant patients than non-pregnant ones ($p=0.018$ and $p=0.003$, respectively) (Table 4).

Discussion

The results of this study demonstrated that late follicular phase progesterone levels were stable during the cycles of pregnant patients irrespective of the protocol. Late follicular phase progesterone levels were shown to be higher in pregnant patients in antagonist cycles when compared to agonist cycles. The number of top-quality embryos was the most important factor that determined the clinical pregnancy in both groups.

According to the two-cell two-gonadotrophin theory [17], progesterone is produced by the conversion of pregnenolone through the action of 3β -hydroxysteroid dehydrogenase (3β HSD) in granulosa cells. It is then transported to the theca cells, where it is metabolized into androgens and eventually to estrogen through the activity of C17 hydroxylase present only in theca cells. Progesterone is an intermediate product in the estrogen production pathway. During the early follicular phase, LH acts exclusively on theca cells to stimulate both 3β HSD and C17 hydroxylase in a balanced manner. However, during the late follicular phase, LH acts not only on theca cells but also its action on granulosa cells becomes evident with the expression of an

increasing number of LH receptors on granulosa cells of growing follicles. With the addition of the stimulatory effect of LH on 3β HSD in granulosa cells, they become another source of increasing progesterone production. In this steroidogenic pathway, estrogen is the end product while progesterone is the intermediate one. Therefore, progesterone measured during the late follicular phase reflects the function of the mature and growing mass of granulosa cells [18].

The detrimental effect of late follicular phase progesterone elevation is thought to be exerted through action on the endometrium [3,10,11,19,20]. However, there are still questions regarding its mechanism of action. The late follicular phase progesterone rise produces an asynchrony between endometrial maturation and the embryo, which eventually causes a reduction in implantation rates. Endometrial gene expression studies provide more direct evidence about the effects of progesterone on the endometrium. Two recent studies reported that when serum progesterone at the time of hCG administration is >1.5 ng/ml, the gene expression profile is modified and expression of more than 100 genes is significantly dysregulated [13,14], genes that are implicated in cell adhesion, developmental processes or the immune system. However, different cut-off values determined for high, normo and poor responders suggest that different mechanisms other than endometrial advancement could have a potential role in its detrimental effects on IVF outcome. Otherwise, a single threshold value would be sufficient to explain its effects in all groups.

Another mechanism, other than the progesterone rise in the single progesterone measurement, might be the duration of the late follicular phase progesterone elevation. Huang et al. [21] studied 1784 patients undergoing IVF/ICSI cycles retrospectively and grouped the patients according to the duration of progesterone elevation during the follicular phase, defined as >1.0 ng/ml. They demonstrated that the clinical pregnancy rate was significantly decreased in women with longer elevated serum P levels, independent of the protocol used and the ovarian response. It has been suggested that a single determination of serum progesterone on the day of hCG could be less informative than

Table 2. Embryo transfer day 3 and day 5 outcomes in patients with and without progesterone elevation on the hCG day.

	$p \leq 2$ ng/ml (n=42)	$p > 2$ ng/ml (n=76)	p Value
Day 3 (n, %)			
Clinical pregnancy rate	17/70 (24.3)	2/7 (28.6)	0.80
Day 5 (n, %)			
Clinical pregnancy rate	48/103 (46.6)	9/21 (42.9)	0.75

Table 3. Controlled ovarian stimulation characteristics of pregnant and non-pregnant normo-responder patients in antagonist cycles.

	Pregnant (n=34)	Non-pregnant (n=49)	p Value	95% CI
P on the hCG day pre-measurement (ng/ml)	1.37 ± 0.1	1.2 ± 0.09	0.13	-0.45 to 0.11
P on the hCG day (ng/ml)	1.51 ± 0.09	1.38 ± 0.08	0.17	-0.39 to 0.13
E2 on the hCG day (pg/ml)	2482.5 ± 1253.9	2263.5 ± 176	0.39	-770.8 to 332.8
Number of retrieved oocytes	15.2 ± 1.2	14.1 ± 0.9	0.46	-4.22 to 2.02
Number of MII oocytes	10.9 ± 0.9	9.9 ± 0.8	0.35	-3.52 to 1.50
Fertilization rate	51.3 ± 3.9	47.8 ± 3.5	0.51	-14.19 to 7.13
No. of top-quality embryos	3.05 ± 1.67	2.04 ± 0.2	0.007*	-1.75 to 0.289
Endometrial thickness on the day of embryo transfer	10.7 ± 0.4	10.2 ± 0.3	0.35	-1.43 to 0.46

*Statistically significant, data were presented as mean ± SE.

Table 4. Controlled ovarian stimulation characteristics of pregnant and non-pregnant normo-responder patients in long agonist cycles.

	Pregnant (n=42)	Non-pregnant (n=76)	p Value	95%CI
P on the day hCG day pre-measurement (ng/ml)	1.11 ± 0.07	1.19 ± 0.06	0.43	-0.1 to 0.279
P on the hCG day (ng/ml)	1.25 ± 0.07	1.37 ± 0.07	0.55	-0.09 to 0.337
E2 on the hCG day (pg/ml)	3486.1 ± 241.6	3740.88 ± 252.8	0.90	-507.6 to 1017.1
Number of retrieved oocytes	15.7 ± 1.2	17 ± 1	0.53	-1.95 to 4.65
Number of MII oocytes	11.7 ± 0.71	11.9 ± 0.8	0.68	-2.21 to 2.65
Fertilization rate (%)	57.9 ± 2.8	46.09 ± 2.7	0.003*	-20.19 to 3.389
No. of top-quality embryos	2.6 ± 0.23	2.0 ± 0.19	0.018*	-1.19 to 0.047
Endometrial thickness on the day of embryo transfer (mm)	10.0 ± 0.32	10.2 ± 0.27	0.82	-0.623 to 1.09

*Statistically significant, data presented as mean ± S.E.

multiple assessments during the days preceding hCG. The prospective study published by Kyrou et al. [22] revealed that progesterone exposure during the ovarian hyperstimulation is associated with a decreased probability of ongoing pregnancy. However, hCG day progesterone level is not related to achievement of pregnancy. Rather than a single measurement, analysis of the change in the last 48 h of the stimulation, as determined in our study, could be a more informative option. More stable values of progesterone observed in pregnant cycles during the last 48 h of stimulation, which is different from the fluctuations observed in non-pregnant cycles, could be another factor affecting the outcomes.

The management of the patients who had progesterone elevation at the late follicular phase is still controversial. Some of the authors revealed no negative impact of progesterone elevation on the pregnancy rates in women performing blastocyst transfer, whereas others did not demonstrate any improvement of blastocyst transfer [23–26]. Another suggested management option for these patients is freeze all policy. However, this option mainly depends on the embryo quality of the patient and laboratory equipment of the IVF center.

The main limitation of this study was its case-controlled design. However, to the best of our knowledge, this is the first study that demonstrates an effect of change in progesterone level in the last 48 h of stimulation rather than a single level above the determined threshold.

As a conclusion, although there are questions regarding the effects of late follicular phase progesterone rise, the assessment change in the last 48 h of the stimulation cycle may be more informative than a single measurement. However, more studies are needed to draw strong conclusions.

Declaration of interest

The authors declare no conflicts of interest.

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