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Research Article

Prognostic Value of Basal and Preovulatory Hormone Levels for Determining Fertility Outcome in Women Undergoing *In Vitro* Fertilization and Embryo Transfer

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Abstract

Aim: This study was planned to test the role of FSH and estradiol-17beta (E2) levels evaluated on the third day of the menstrual cycle and the progesterone levels measured on hCG day in predicting fertility outcomes in women undergoing *in vitro* fertilization and embryo transfer (IVF-ET). We also evaluated whether the predictive ability of FSH level on cycle day 3 can be enhanced by level of E2 on cycle day 3.

Method: This study was performed on patients who applied to the Dr Zekai Tahir Burak Hospital IVF unit between October 1991 and February 1997. 990 IVF cycles were retrospectively analyzed in 882 infertile patients. In addition to basal FSH and E2 levels, the predictive value of progesterone levels measured on the day of HCG was tested for pregnancy rates. The cut-off value for basal FSH was 14 mIU/ml, the cut-off value for basal E2 was 80 pg/ml, while the cut-off value for progesterone was considered as 0.9 ng/ml. In addition to demographic features and hormone profile, total number of ampoules used, the number of follicles collected, mature oocyte count, fertilization rates, cycle cancellation rates and clinical pregnancy rates were examined in all patients.

Results: The clinical pregnancy rate in patients with basal E2 level < 80 pg/ml was 14.4% per cycle and the rate of clinical pregnancy in patients with E2 level > 80 pg/ml was 13.8% ($p > 0.05$). Pregnancy rate per ET was 19.2% and 18.3% ($p > 0.05$), respectively. Cycle cancellation rates were 4.8% for those with E2 < 80 pg/ml and 5.2% ($p > 0.05$) for those with E2 > 80 pg/ml. There were no differences between the groups in terms of age and total number of rFSH ampoules. Clinical pregnancy rate was 14.7% per cycle in patients with basal FSH < 14 mIU/ml, and no pregnancy was obtained in patients with basal FSH > 14 mIU/ml. In addition, the cancellation rates were 4% and 29.6%, respectively (p: 0.001). The fertilization rate in the group with progesterone value < 0.9 ng/ml on HCG day was 73.6% while the fertilization rate in the group with progesterone value > 0.9 ng/ml was 79.9% ($p < 0.05$). The cancellation rates were 4% and 1.7% ($p < 0.05$). In women with progesterone levels were higher than 0.9 ng/ml, fertilization rates were high and the rate of cancellation was low but there was no difference between the two groups in terms of clinical pregnancy rates.

Conclusions: Detection basal FSH bigger than 14 mIU/ml indicates poor stimulation response and low IVF pregnancy outcomes. We also found that basal E2 level alone did not give anything more than the prognostic value provided by FSH alone. Progesterone elevation detected on HCG day no adverse effect on clinical course in IVF-ET applications.

Keywords: *Prognostic Value; Fertility Outcome; In Vitro Fertilization; Embryo Transfer*

Introduction

Measurement of the basal FSH level is one of the main parameters to predict ovarian reserve in reproductive age women. High levels of basal Follicle stimulating Hormone (FSH) appear to correlate with low responses of ovary to controlled ovarian stimulation [1]. Likewise, basal serum estradiol (E2) levels show stage of follicular growing, and higher basal E2 concentrations associate with follicular asynchrony. Early rise of E2 can be a main finding of the shortened follicular phase often seen before menopause [2,3].

Progesterone elevation during the late follicular phase of ovarian stimulation negatively affects the fertility outcome. High progesterone levels induce advanced endometrial maturation and disturb endometrium receptivity. Likewise high progesterone impairs developing oocyte and embryo. Increased FSH-stimulation towards the end of the follicular phase of ovarian stimulation is the main culprit of progesterone elevation. Main approaches for preventing progesterone elevation are the individualization of ovarian stimulation protocol, avoidance of prolonged stimulation and freeze-all-policy [4,5].

However, it is still unclear whether evaluation of serum FSH, E2 and progesterone levels at the same time may predict the pregnancy outcomes of women undergoing IVF-ET [3]. This study was planned to test the role of FSH and estradiol-17beta (E2) levels evaluated on the third day of the menstrual cycle and the progesterone levels measured on hCG day in predicting fertility outcomes in women undergoing assisted reproduction. We also evaluated whether the predictive ability of FSH level on cycle day 3 can be enhanced by levels of E2 on cycle day 3. Thus, we conducted a retrospective cohort study comparing the pregnancy outcomes of IVF women at different FSH, E2 and with different levels progesterone.

Materials and Methods

A single-center retrospective study was performed on patients who initiated IVF cycles between October 1991 and February 1997 in Dr. Zekai Tahir Burak Hospital IVF unit. Study groups were identified from an electronic medical records database according to the patient's basal FSH history. Patients were treated with long agonist protocol. Total gonadotropin dose was calculated for each patient in ampules. We assessed the effect of a patient's basal FSH and E2 measurements and progesterone levels on the day of hCG on her future fertility outcomes, carefully focusing on 990 IVF cycles in 882 infertile patients. Age, basal FSH, basal E2, total recombinant FSH (rFSH) ampul count, peak E2, progesterone on hCG day, follicle number, mature oocyte count, fertilization rate, cycle cancellation rate and clinical pregnancy rates were examined in all patients. Serum progesterone level was measured by Ciba Corning ACS 180 method, E2 level by Chemiluminescence method and FSH level by heterogen ELISA CobasCore FSH EIA methods. For basal FSH, 14 mlU/ml cut-off value was accepted. For basal E2 level 80 pg/ml is considered as cut-off value. The cut-off value for hCG was considered as 0.9 ng/ml.

Statistical analysis

The Statistical Package for Social Sciences, version 21.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Individual group parameters were assessed with one-sample Kolmogorov-Smirnov Z test and were found to be abnormally distributed. Statistical comparisons between groups were performed by nonparametric Student t-test and χ^2. Data are presented as mean ± standard deviation (SD). For all comparisons, statistical significance was defined by P Value ($p < 0.05$).

Results

We evaluated the basal E2 level in 880 IVF cycles. The results of baseline parameters and pregnancy outcomes of patients in low FSH and high FSH groups were presented in tables 1 and 2. Controlled ovarian hyperstimulation was performed in 628 cycles with basal E2 level of < 80 pg/ml and 252 cycles with basal E2 > 80 pg/ml. The clinical pregnancy rate was 14.4% in the in patients with basal E2 level < 80 pg/ml and the rate of clinical pregnancy in patient with E2 level > 80 pg/ml was found to be 13.8%. The difference between two groups

were not significant (p > 0.05). Clinical pregnancy rates per cycle were 14.7% in patients with basal FSH level < 14 mlU/ml. In patients with basal FSH level > 14 mlU/ml, pregnancy could not be achieved. The fertilization rate was found to be 76.5% in the cycles with basal FSH level < 14 mlU/ml and in the patients with basal FSH level > 14 mlU/ml it was 37% (p < 0.01). The cycle cancellation rate was noted as 4% and 29.6% (p < 0.01).

	FSH <14 mlU/ml		P	FSH >14 mlU/ml		P
	E2 < 80 pg/ml	E2 > 80 pg/ml		E2 < 80 pg/ml	E2 > 80 pg/ml	
Number of cycles	615	238		14	13	
Age	32.3 (4.8)	32.6 (4.6)	NS	34.5 (4.3)	35.2 (4.4)	NS
Total Number of Bulbs	36.27 (30.63)	34.96 (14.04)	NS .	51.86 (26.99)	42.62 (19.13)	*<0.05
Max E2	2175 (1518)	1992 (1011)	NS	1728 (1147)	834 (616)	NS
Day 3 FSH	7 (3)	7 (3)	NS	16 (1)	18 (3)	NS
Day 3 E2 *	50.6 (16.6)	137.2 (82.5)	*<0.05	51.1 (17.4)	142 (74.7)	*<0.05
Day 3 LH	7 (5)	8 (6)	NS	10 (6)	24 (21)	NS
P on hCG day	1 (2)	1 (3)	NS	1 (0)	1 (1)	NS
Endo HCG	11 (2)	10 (2)	NS	10 (2)	11 (3)	NS
Follicle 9 - 15 mm	4.5 (3.8)	4.5 (3.7)	NS	2.9 (2.5)	1.5 (2.2)	*<0.05
Follicle > 15 mm	7 (4)	6 (3)	NS	4 (4)	2 (3)	*<0.05
Grade 1 oocyte	5 (4)	5 (4)	NS	3 (3)	1 (1)	*<0.05
Total oocyte number	7 (5)	6 (4)	NS	4 (5)	1 (2)	*<0.05
Fertilization rate (ET)	76.1%	77.8%	NS	35.7%	38.5%	NS
Cancellation rate*	4.6%	2.9%	*<0.05	14.3%	46.2%	*<0.05
Clinical Pregnancy rate per cycle	14.8%	17%		-	-	

Table 1: *Fertility outcome of subjects according to basal FSH and E2.*

NS: Not significant.

**: The significant difference between the groups p < 0.05.*

	P < 0.9 ng/ml	P > 0.9 ng/ml	P
Number of Cycles	379	473	
Age	33.2 (4.7)	31.6 (4.7)	0.16
Day 3 FSH*	7.4 (3.3.)	6.9 (3)	0.017*
Total Number of Bulbs	36.8(15.5)	35.3 (16.7)	0.193
Peak E_2*	1958 (1749)	2302 (950)	0.001*
P on hCG day*	0.61 (0.21)	1.86 (2.36)	0.001*
Follicle 9 - 15 mm*	4.1 (3.4)	8 (4.0)	0.006*
Follicle > 15 mm*	5.9 (3.4)	6.9 (4.0)	0.001*
Grade 1 oocyte*	4.7 (4.0)	5.5 (4.6)	0.01*
Total oocyte*	5.9 (3.9)	7.4 (4.7)	0.001*
Fertilization rate*	%73.6	%79.9	0.029*
Cancellation rate*	%4	%1.7	0.0425*
Clinic pregnancy rate	%12.4	%15	0.408

Table 2: *Fertility outcome of subjects according to progesterone on hCG day.*

**: The significant difference between the groups p < 0.05.*

379 of the 852 cycles (44.5%) had a progesterone value below 0.9 ng/ml. In 473 cycles (55.5%), progesterone was elevated on HCG day. The fertilization rate was 73.6% in the p < 0.9 ng/ml group and 79.9% in the p > 0.9 ng/ml group (p < 0.05). Cancellation of the cycle was 4% in the p < 0.9 ng/ml group and 1.7% in the group with p > 0.9 ng/ml (p < 0.05). In the group with p > 0.9 ng/ml, fertilization rates were high and the rate of cancellation was low, but there was no difference in clinical pregnancy rates between the two groups. The clinical pregnancy rate in the group with p < 0.9 ng/ml was 12.4, whereas it was 15% in the group with p > 0.9 ng/ml.

We found that the high FSH was the good predictor of cycle cancellations and the number of oocytes retrieved. However, we did not detect any deleterious effect in pregnancy or live birth rates due to high progesterone levels. In patients with elevated FSH levels bigger than 14 mIU/mL on cycle day 3, a low oocyte yield was achieved and a high number of ampules of rFSH was necessary. Their cancellation rate was also high than those in women with FSH level smaller than 14 mIU/mL. In women with normal basal FSH levels but E2 levels bigger than 80 pg/ml predicted a high cancellation rate and a low oocyte yield but the difference failed to reach statistical significance. Patients with both normal FSH levels and low E2 levels on cycle day 3 and normal progesterone levels on hCG day fared best.

Discussion

High FSH levels measured on day 3 of cycles are associated with more frequent *in vitro* fertilization (IVF) cycle cancellations and fewer eggs being retrieved. Ovarian response to rFSH preparations is negatively correlated with day 3 FSH levels [1]. FSH levels correlate with oocyte retrieval rate independently of age and stimulation protocol [6,7]. Despite this fact, the effect of basal E2 on oocyte retrieval rates is unknown. Likewise, the impact of basal FSH and E2 levels on fertilization, implantation or clinical pregnancy rates are not known exactly [8].

We found that infertile women had much better fertility outcomes than older women regardless of their basal hormone levels and preovulatory progesterone level. In addition to, low oocyte retrieval rate the clinical pregnancy rates declined in women with high basal FSH, even though they had normal E2. Infertile women with high FSH level (> 14 mIU/mL)had a worse clinical pregnancy rate especially with high E2 level (> 80 pg/mL). Interestingly, basal E2 level alone did not give anything more than the prognostic value provided by FSH alone. In women having high progesterone level on hCG day, fertilization rates were high and the rate of cancellation was low. On the other hand, there was no difference in clinical pregnancy rates between the women with normal and high progesterone levels.

Some IVF centers now argue for abandoning FSH measurement for determining ovarian reserve altogether in favor of anti müllerian hormone (AMH) testing [9]. However, recent study conducted by Gingold., *et al*. [10] demonstrated the strong connection between FSH and oocyte retrieval rate after controlling AMH levels. They suggested that in addition to AMH test continue assessment of FSH levels is required. In line with this, the study demonstrates that day 3 FSH levels bigger than 14 mIU/ml predict cycle cancellation, stimulation response and mature oocyte retrieval rates better than basal E2 levels. In view of our results we can suggest that a combination of FSH and E2 couldn't improve predictive potential of FSH on fertility outcome for women undergoing IVF-ET.

Basal E2 levels are consistently smaller than 100 pg/mL in healthy infertile women between D2 and D5 of their cycles [2]. Women having cycles with a basal E2 level ≥ 100 pg/mL are known to have high cancellation rates and poor clinical pregnancy rates [11]. There were no significant differences in the total numbers of yielded oocytes and the number of available embryos, the fertilization rates, between low E2 and high E2 groups. However, the patients with high E2 and FSH levels appeared lower clinical pregnancy rate than the patients with high FSH alone. When our results and literature were evaluated together, the basal FSH level on cycle day 3 is a useful prognostic factor of response to stimulation in IVF patients with normal basal E2 levels. On the other hand, the basal E2 level on cycle day 3 is not a useful prognostic factor of response to stimulation in IVF patients. Likewise, serum progesterone level on hCG day does not have a detrimental effect on fertility outcome. Finally, the clinical pregnancy rate downward trend with high FSH and E2 levels. This result suggests that, high FSH and high E2 may disturb both the quality of embryos and pregnancy rate. However, the level of progesterone does not make important sense for pregnancy outcomes.

Conclusions

Detection basal FSH bigger than 14 mIU/ml indicates poor stimulation response and low IVF pregnancy outcomes. Measurement of basal E2 level alone did not give anything more than the prognostic value provided by FSH alone. Progesterone elevation detected on hCG day no adverse effect on clinical course in IVF-ET applications.

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