The Predictive Value of Estradiol Response After Human Chorionic Gonadotropin Administration on the Outcome in IVF-ET Cycles

İN-VİTRO FERTİLİZASYON EMBRYO TRANSFERİ SİKLUSLARINDA HCG UYGULAMASI SONRASI ESTRADİOL CEVABI SİKLUS BAŞARISINI ÖNGÖREBİLİR Mİ?

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Summary

Objective: To analyse the effect of the changes in serum estradiol (E2) concentrations after human chorionic gonadotopin administration(HCG) on fertilization rate and pregnancy rate in in-vitro fertilization embryo transfer(IVF-ET) cycles.

Setting: Ege University, Family Planning, Infertility Research and Treatment Center, Bornova, İzmir, Turkey

Matherial and Method: Two-hundred-forty-eight patients who had undergone IVF-ET were enrolled into the study. The patients were grouped according to the ratio of serum E2 levels before and after HCG administration; group-1 consisted of the patients who had an increase in E2 of >10%, group-2 with E2 levels remained between a gain and loss of 10%, and group-3 responders exhibited a >10% decrease in their E2 levels after HCG. The primary outcome measures included the oocyte quality, the fertilization rates and the clinical pregnancy rates.

Results: There was no difference in terms of the mean number of metaphase-II oocytes picked up among the groups (7.4, 8.3, 8.5, repectively),(p=0.248). The fertilization rates in group-1, group-2, and group-3 were found to be similar(76%, 78%, 80%, respectively),(p=0,833). The clinical pregnancy rates in group-1, group-2, and group-3 were 35.0% (50/143), 32.9.0% (26/79), and 30.8% (8/26), respectively and there was no statistically significant difference (p=0.896).

Conclusion: In our study population, the results do not ascribe any predictive significance of E2 response after HCG administration to oocyte quality, fertilization rates and clinical pregnancy rates in IVF-ET cycles.

Key Words: Human Chorionic Gonadotropin, E2-response,IVF-ET Outcomes

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Özet

Amaç: İn-vitro fertilizasyon embryo transferi(IVF-ET) sikluslarında human chorionic gondotropin (HCG) uygulandıktan sonra estradiol (E2) oranlarında gözlenen değişim derecesine göre fertilizasyon oranlarının ve gebelik oranlarının etkilenip etkilenmediğini araştırmak.

Çalışmanın Yapıldığı Yer: Ege Üniversitesi, Aile Planlaması, İnfertilite Araştırma ve Uygulama Merkezi, Bornova, İzmir

Materyal ve Method: IVF-ET uygulanan 248 olgu çalışma kapsamına alındı. Hastalar HCG uygulama öncesi ve sonrasında ölçülen estradiol seviyelerinin oranlanmasına göre sınıflandırılarak E2 düzeyi %10'dan fazla artanlar grup-1, E2 seviyesi öncekine göre %10'dan daha az artan yada azalanlar grup-2 ve E2 düzeyi öncekine göre %10'dan fazla düşenler grup-3 olmak üzere 3 gruba ayrıldı. Gruplarda, alınan oositlerin kaliteleri, fertilizasyon oranları ve klinik gebelik oranları karşılaştırıldı.

Bulgular: Gruplar arasında elde edilen ortalama metafaz-II oosit sayılarında anlamlı fark yoktu (sırasıyla; 7.4, 8.3, 8.5), (p=0.248). Fertilizasyon oranları her üç grupta da benzerdi; (sırasıyla; %76, %78, %80). Klinik gebelik oranları gruplarda sırasıyla %35.0 (50/143), %32.9 (26/79) ve %30.8 (8/26) bulundu ve istatistiksel olarak anlamlı değildi.

Sonuç: Çalışma grubumuzda elde edilen sonuçlara göre IVF-ET sikluslarında HCG uygulaması sonrası E2 seviyesinde meydana gelen değişiklikler ile oosit kalitesi, fertilizasyon oranları ve klinik gebelik oranları arasında korelasyon saptanamadı.

Anahtar Kelimeler: Human Chorionic Gonadotropin, E2-cevabı, IVF-ET başarısı

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Accurate prediction of a successful outcome during controlled ovarian hyperstimulation (COH) remains an unachieved goal. Methods previously reported to have some usefulness in the assesment of ovarian reserve include the measurement of baseline cycle day 3 estradiol, FSH, inhibin B levels (1-4). In addition, clomiphene citrate (CC) test, estradiol patterns during gonadotropin stimulation, and responses to GnRH agonists are reported to predict ovarian responsiveness to COH (5-7). Currently, COH is monitored by repeated pelvic ultrasonography or serum estradiol measurements. It is believed that transvaginal sonographic findings reflect growth, whereas serum estradiol levels primarily detect functional activity of follicles. Use of the serum estradiol levels detected after the initiation of gonadotropin stimulation may act as an early marker of ovarian response which may help in deciding whether to proceed with ongoing cycle (9). Several studies have shown significantly lower implantation and pregnancy rates in cycles with high serum estradiol concentrations (10), whereas others have found no adverse effects (11). The purpose of this study was to examine the impact of the changes in serum estradiol (E2) concentrations after human chorionic gonadotopin administration (HCG) on fertilization rate and pregnancy rate in IVF-ET cycles.

Materials and Methods

Two-hundred-forty-eight patients who had undergone in vitro fertilization and embryo transfer in the second half of 2001 in Ege University Family Planning, Infertility Research and Treatment Center were enrolled into the study. Infertility reasons were andrologic factor, tuboperitoneal factor, endometriosis, and idiopathic infertility.

Gonadotropin releasing hormone analog Triptorelin acetate 0,1 mg/day (Decapeptyl 0,1 mg solution, subcutaneous injection, ER-KIM Endustri-Ferring) was used for pituitary down regulation and controlled ovarian hyperstimulation was achieved with recombinant follicle stimulating hormone or human menopausal gonadotropin (Metrodin-Pergonal, Serono) according to the patients previous findings. The stimulation was continued until the follicles were at least 18 mm in diameter and then ovulation was triggered by administration of 10.000 IU hCG (Profasi-Serono or Pregnyl-Organon). Approximately 36 hours after the administration of hCG, oocytes were picked up by tranvaginal sonographic assistance. The oocytes were morphologically graded according to the oocyte-cumulus complexes. Embryo transfer was performed 48-72 hours later. Luteal phase was supported with transvaginally given progesteron, 600mg/day (Progestan 100mg capsul, Kocak Pharmacy) and hCG injections every three days until 9th week of ongoing pregnancy. Pregnancy was confirmed in patients with hCG levels over 20 mIU/mL and recorded.

The patients were grouped according to the ratio of serum E2 levels before and after HCG administration of which group-1 consisted of the patients who had an increase in E2 of >10%, group-2 with E2 levels remained between a gain and loss of 10%, and group-3 responders exhibited a >10% decrease in their E2 levels after HCG. Then the patients classified according to the rates of HCG day estradiol levels to baseline estradiol levels; patients with the rates ≤ 60 pg/mL : group-A and the patients with the rates > 60 pg/mL : group-B). The primary outcome measures included the oocyte quality, the fertilization rates and the clinical pregnancy rates.

Estradiol titers were calculated by Automated Chemiluminescense System(ACS):180 estradiol-6 II with %2 variation.

Data were expressed as mean ± standart deviations (SD), or means with %95 confidence interval (CI), where appropriate. Differences in outcome measures between subsets of patients thus generated were examined by analysis of variance (ANOVA), with Duncan's significant difference test for post hoc comparisons. The difference on pregnancy outcomes between the groups were examined by Chi square test. P value <0.05 was considered statistically significant. The statistical analysis was carried out using the Statistical Pack-

age for Social Sciences (SPSS) Version 10.0 for Windows (SPSS Inc, USA).

Results

The mean (±SD) patient age was 29.9±3.5 years (range,20-36 years) and three groups were homogeneous in terms of age (p=0.344).

There was no difference in terms of the mean number of metaphase-II oocytes picked up among the groups (7.4, 8.3, 8.5, respectively), (p=0.248). The fertilization rates in group-1, group-2, and group-3 were found to be similar (76%, 78%, 80%, respectively), (p=0,833). The clinical pregnancy rates in group-1, group-2, and group-3 were 35.0% (50/143), 32.9.0% (26/79), and 30.8% (8/26), respectively and there was no statistically significant difference (p=0.896) (Table 1).

There was also no statistically significant difference between group-A and group-B on clinical pregnancy rates and fertilization rates (Table 2).

Table 1. Relation between E2 patterns and IVF outcomes

Response*	No. of patients	Patient age	No. of mature ocytes	Fertilizaton rate (%)	PR, ongoing (%)
Increase	143	29.7±3.7	7.4±4.4	76	35.0
Plateau	79	30.1±3.6	8.3±4.2	78	32.9
Decrease	26	30.4±3.1	8.5±5.3	80	30.8

Note: Values are expressed as mean ± standard deviation.
*Response >10% in E2 taken as increase, E2 levels remained between a gain and loss of 10% taken as plateau, <10% in E2 taken as decrease on day of HCG injection
No statistically significant difference seen between E2 patterns and IVF outcomes in the groups.

Table 2. Outcome of the patients in group-A and group-B

	Group-A (n=172)	Group-B (n=76)	P value
Fertilization Rate(%)	78	75	0.516 (NS)*
Pregnancy Rate(%)	32	38,5	0.195 (NS)

NS: Not Significant

Discussion

Stewart et al.(12) found a significant difference in estradiol concentrations as early as day 6 after the luteinizing hormone (LH) surge between conception and non-conception cycles in fertile women undergoing donor insemination. The day 6 rise in luteal estradiol in conception cycles compared to non-conception cycles was also noted in a group of 32 women attempting spontaneous pregnancy (13). These findings provide evidence that a trophoblastic stimulus is present before implantation and the ovary is capable of responding appropriately by enhancing steroid production. In contrary, Nylund et al.(14) found no difference in the estradiol concentrations in the mid-luteal phase between conception and non-conception cycles. However, Sharara et al.(15) revealed that the magnitude of the decline in estradiol concentrations between the days of HCG administration and 8 days later, measured by the ratio of peak estradiol to midluteal estradiol, did predict IVF outcome. They also underlined that a sharp decline in the mid-luteal estradiol, defined as an elevated peak estradiol to mid-luteal estradiol ratio >5, resulted in a significantly lower ongoing implantation rate and pregnancy rate.Yang et al.(16) investigated the influence of various estradiol (E2): oocyte ratios on reproductive outcome in women undergoing in vitro fertilization and tubal embryo transfer (IVF-TET) and concluded that IVF-TET cycles with an elevated E2: oocyte ratio correlated with lower pregnancy and implantation rates. They also underlined that the poor reproductive outcome possibly was due to the relatively high E2 concentration, which might have a detrimental effect on endometrial receptivity. Some other studies revealed that low late-midluteal estradiol levels have worsened the IVF outcomes (17,18) however Hutchinson-Williams et al.(19) measured both estradiol and progesterone levels every 3 days during the luteal phase in IVF patiens and found that estradiol and progesterone both fell in conception and nonconception cycles.

In spontaneous menstruel cycles of fertile women, serum E2 levels decrease after the LH surge, a likely reflection of decreased production

of thecal androgens and a concurrant fall in granulosa cell aromatase activity. In contrast, in a group of women specifically with tubal infertility, a decrease in serum E2 values after exogenous HCG administration, despite normal fertilization and cleavage rates, has been associated with poor success during IVF and the investigators suggested cancellation of an oocyte harvest if the E2 level dropped (20).

We hoped to determine whether the E2 response after HCG administration might predict success in IVF. In our study, the response after HCG was not predictive of oocyte quality, fertilization rates, or implantation rates in the groups. However, the trend toward higher fertilization rates with a plateau or drop in E2 level after HCG day may indicate better follicular maturity. Meyer et al.(21) similarly failed to demonstrate such a correlation between the serum E2 response before and after HCG administration and cycle outcomes in IVF cycles.

In conclusion, woman's E2 response to HCG administration do not ascribe any predictive significance on the oocyte quality, the fertilization rates and the clinical pregnancy rates in IVF-ET cycles.

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