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Does the decrease in E2 levels between the trigger of ovulation and embryo transfer affect the reproductive outcome in IVF-ICSI cycles?

HCG enjeksiyonu ve embriyo transferi arasındaki E2 seviyelerindeki düşüş, IVF-ICSI döngülerinde üreme sonucunu etkiler mi?

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Abstract

Objective: This study aimed to evaluate the effect of the rate of decline in serum estradiol (E2) levels between hCG injection and the day of embryo transfer (ET) on the success of assisted reproductive technology (ART) in women with infertility of different etiologies.

Materials and Methods: Women 20-45 years of age who underwent a standard GnRH antagonist or long agonist protocol and fresh ET during day 3 of their first ART cycle were included. Group 1 was diagnosed with low ovarian reserve, group 2 comprised high ovarian responders, and group 3 consisted of normal responders. Both groups were divided into four subgroups according to the decrease in E2 levels between the day of hCG injection and the day of ET. Subgroup A patients had a decrease of <20%, subgroup B a decrease of 20-40%, subgroup C a decrease of 41-60%, and subgroup D a decrease >60%. The primary outcome measure was the effect of an E2 decline, based on the measurement of E2 on the day of hCG administration and day of ET, on the implantation rate. The secondary outcome was the change in E2 values in these three groups.

Results: The study was conducted on 1.928 women. Of these, 639 were poor responders (group 1), 502 were high responders (group 2), and 787 women had a normal ovarian response (group 3). Patients with a 60% decrease in their E2 levels on the ET day after hCG had a lower live birth rate (LBR) and higher miscarriage rate (MCR), except normoresponders, in whom a similar decline was significant only with respect to MCR.

Conclusion: We indicate that high ovarian responders who underwent fresh ET cycles with a 60% decrease in their E2 levels on the ET day after human chorionic gonadotropin had lower LBRs and higher miscarriage. However, in normoresponder women, this decline was only significant in miscarriage.

Keywords: E2 decline, high ovarian response, live birth rate, low ovarian reserve, miscarriage rate

Öz

Amaç: Bu çalışma, farklı etiyolojilere bağlı infertilitesi olan kadınlarda embriyo transfer günü olan hCG enjeksiyonu arasında serum E2 düzeylerindeki düşüş hızının yardımcı üreme teknolojisi (ART) başarısına etkisini değerlendirmek amacıyla yapılmıştır.

Gereç ve Yöntemler: Ocak 2011-Aralık 2018 tarihleri arasındaki veriler Tüp Bebek Kliniği hastane kayıtlarından alınmıştır. İlk ART sikluslarının 3. gününde standart bir GnRH antagonisti veya uzun agonist protokolü ve taze embriyo transferi uygulanan 20-45 yaş arası kadınlar dahil edildi. Grup-1 yumurtalık rezervi düşük olanlardan, Grup-2 yüksek yumurtalık yanıtı verenlerden, Grup-3 normal yanıt verenlerden oluştu. Her iki grup hCG enjeksiyon

PRECIS: High ovarian responders who underwent fresh ET cycles with a 60% decrease in their E2 levels on the ET day after HCG had lower live birth rates and higher abortion rates. However, in normoresponder women, this decrease was significant only in abortion rates. In patients with low ovarian reserve, the change in E2 between HCG and the third day ET had no clinical effect.

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günü ile embriyo transfer günü arasında E2 düzeyindeki azalmaya göre dört alt gruba ayrıldı. Alt grup A hastalarında <%20, alt grup B'de %20-40, alt grup C'de %41-60 ve alt grup D'de >%60 azalma vardı. Hastaların demografik özellikleri ve tüp bebek sonuçları çıkarıldı.

Bulgular: Çalışma 1.928 hasta ile yapıldı. Bunlardan 639'u düşük over yanıtı veren (grup 1), 502'si yüksek over yanıtı veren (grup 2) ve 787 kadının normal yumurtalık yanıtı vardı (grup 3). hCG'den sonraki embriyo transfer gününde E2 düzeylerinde %60 azalma olan hastaların düşük doğum ağırlığı daha düşük ve düşük yapma oranı daha yüksekti, ancak normo-yanıt verenler hariç benzer bir düşüşün sadece düşük yapma oranında anlamlı olduğu gösterilmiştir.

Sonuç: İnsan koryonik gonadotropinden sonraki embriyo transfer gününde E2 seviyelerinde %60'lık bir düşüşle taze embriyo transfer siklusları uygulanan yüksek over yanıtlı kişilerin, daha düşük canlı doğum oranlarına ve daha yüksek düşük yapma oranlarına sahip olduğunu belirtiyoruz. Ancak, normo yanıt veren kadınlarda bu düşüş yalnızca düşük yapmada anlamlıydı.

Anahtar Kelimeler: E2 düşüşü, yüksek over yanıtı, canlı doğum oranı, düşük over rezervi, düşük yapma oranı

Introduction

Implantation is the most important step in assisted reproductive technologies (ARTs), but the process is still poorly understood. However, it has been shown that implantation is strongly related to endometrial receptivity, which in turn is affected by serum estradiol (E2) and progesterone (P) levels[1-3]. The results clearly showed that very low or supraphysiological E2 levels have a negative impact on the reproductive outcome[4,5].

E2 levels that become supraphysiological following ovarian hyperstimulation during gonadotropin therapy may decline promptly after therapy is stopped prior to the hCG injection. This response is due to the withdrawal of the injected gonadotropins and aspiration of the granulosa cells during the oocyte retrieval process. The decrease is more severe in high-responder patients and may lead to low CPRs due to deteriorating endometrial receptivity. Accordingly, patients with early and rapid declines in P levels receive luteal support during the early stages of In vitro fertilization (IVF)[6]. However, whether the decrease in E2 levels affects endometrial receptivity or the success of treatment on the day of hCG injection and ET is unclear.

The aim of this study was to evaluate the effect of the rate of decline in serum E2 levels between hCG injection and the day of ET on the success of ART in women with infertility of different etiologies. In a secondary analysis, these findings were evaluated in three groups of patients with a poor, normal, or high response to gonadotropin therapy.

Materials and Methods

This study was a retrospective, single-center cohort trial at the IVF clinic of the University of Health Sciences School of Medicine, Etlik Zubeyde Hanım Research and Training Hospital (Turkey). The study period was from January 2011 to December 2018. The study protocol was approved by the hospital ethics committee (Etlik Zubeyde Hanım Research and Training Hospital; no: 90057706-799, date: 19.02.2019). Signed informed consent was obtained from all patients.

Women 20-45 years of age who underwent a standard gonadotropin-releasing hormone (GnRH) antagonist or long agonist protocol and fresh ET during day 3 of their first ART cycle were included in the study. Patients who had an organic pathology involving the uterus and/or endometrium or whose treatment protocol differed from antagonist or long luteal agonist protocols for ovarian hyperstimulation were excluded, as were those with previous IVF-ICSI cycles, who currently had a freeze-thaw cycle, or who underwent day 5 ET. To take advantage of the participants, we did not exclude patients we could not follow up until birth.

In our study population, patients who underwent ET on day 3 and had an antral follicle count (AFC) <11, a serum anti-Müllerian hormone (AMH) level <1.1 ng/mL, and <4 collected oocytes[7,8] were diagnosed with low ovarian reserve and assigned to group 1. Group 2 comprised high ovarian responders who met the inclusion criterion and had a peak E2 level >3000 pg/mL on the day of hCG administration, >15 retrieved oocytes, or a basal AFC >10[9]. Patients with E2 values above 4000[10] were given an agonist trigger for OHSS prophylaxis. Group 3 consisted of normal responders with a peak E2 level of 500-3000 pg/mL on the day of hCG administration, 5-15 retrieved oocytes, and a basal AFC of 7-10[11].

Each group was divided into four subgroups according to the decrease in E2 levels between the day of hCG injection and the day of ET. Subgroup A patients had a decrease of <20%, subgroup B a decrease of 20-40%, subgroup C a decrease of 41-60%, and subgroup D a decrease >60%[12]. Differences in the implantation rate (IR), CPR, miscarriage rate (MCR), and live birth rate (LBR) among subgroups were assessed.

Age, body mass index (BMI) [weight (kg)/height × height (m^2)], follicle stimulating hormone (FSH), and E2 values on the third day of menstruation, total AFC, duration of infertility (months), E2 levels on the days of hCG administration and ET, number of retrieved oocytes, and number of mature oocytes were recorded.

In conventional protocols, recombinant FSH (Gonal-F, Merck Serono, Germany; Puregon, Organon, the Netherlands) with or without human menopausal gonadotropin (Menogon, Ferring Pharmaceuticals, Germany; Merional, IBSA, Switzerland) was used at doses ranging from 150 IU/day to 450 IU/day in accordance with body mass index, patient age, and the number of antral follicles. Patients underwent pituitary downregulation using the luteal long protocol with a GnRH agonist (Lucrin, Abbott, France) or the GnRH antagonist protocol (Cetrotide, 0.25 mg/day, Serono, Germany). During controlled ovarian hyperstimulation (COH), we monitored serum hormone levels, the size and count of follicles, and endometrial thickness. Recombinant hCG (250 mg Ovidrel; Serono) was administered to trigger ovulation when at least two leading follicles reached ≥18 mm in diameter. Transvaginal ovum pick-up was

performed 34-36 h after ovulatory induction. Oocyte pick-up (OPU) was conducted under general anesthesia, followed by ET on day 3 post-retrieval. Serum E2 levels on the day of hCG administration and on the day of ET were measured using an electrochemiluminescence immunoassay kit (Roche Diagnostics GmbH, Mannheim, Germany). Patients who underwent ET received luteal phase support with a P-containing vaginal gel (90 mg/d twice daily, Crinone 8% vaginal gel, Merck-Serono, Switzerland) after oocyte collection and continued during pregnancy until approximately 12 weeks of gestation.

The primary outcome measure was the effect of an E2 decline, based on the measurement of E2 on the day of hCG administration and day of embryo transfer, on IR (positive β-hCG test ≥10 IU, 10 days after embryo transfer), CPR (presence of an intrauterine gestational sac detected on transvaginal USG), MCR (spontaneous pregnancy loss before 20 weeks of gestation) and LBR (the delivery of a viable infant any time after 24 weeks gestation) in the three groups of patients (normal, high, and poor responders). The secondary outcome was the change in E2 values in these three groups. The decline was graded as <20%, 20-40%, 40-60% and >60%.

Statistical Analysis

SPSS 20 (IBM Corp. released 2011. IBM SPSS Statistics for Windows, version 20.0, Armonk, NY: IBM Corp.) was used to evaluate the data. The data were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk's tests) to determine their normal distribution. A One-Way ANOVA and Kruskal-Wallis test were used to compare continuous variables with a normal and non-normal distribution, respectively. Differences between groups were evaluated using Student's t-test for parametric data and the Mann-Whitney U-test for non-parametric data. Relationships between categorical variables were analyzed using a chi-square test. A p-value <0.05 was considered to indicate statistical significance.

Results

The study was conducted on 1.928 women. Of these, 639 were poor responders (group 1), 502 were high responders (group 2), and 787 women had a normal ovarian response (group 3). The age range of the patients was 20-45 years, and the duration of infertility ranged from 12 to 112 months.

The clinical characteristics of the three groups are presented in Table 1. Patient age, basal FSH and E2 levels were significantly higher in group 1 than in groups 2 and 3. AFC, duration of infertility, E2 levels on the day of hCG injection and day of ET, number of retrieved embryos, number of mature oocytes, and IR, CR, and LBR were significantly lower in group 1 than in groups 2 and 3. Group 2 had the highest IR and CPR, and group 3 the highest LBR. The total number of miscarriages

Table 1. Clinical characteristics of subjects

	Group 1 (n=639)	Group 2 (n=502)	Group 3 (n=787)	p
Age (years)	36.7±7.5[b,c]	28.8±4.6	29.5±4.7	<0.001
BMI (kg/m²)	26.9±5.1	27.4±5.2[c]	25.9±4.9[a,b]	<0.001
Basal FSH (IU/L)	10.8±6.2[b,c]	5.9±2.5	6.9±1.6	<0.001
Basal E2 (pmol/L)	55.8±47.5[b,c]	44.3±18.6	47.5±27.2	0.001
AFC	5.7±3.4[b,c]	22.7±7.1[c]	12.9±6.1	<0.001
Infertility duration (month)	65.0±64.7[b,c]	81.1±50.2[c]	69.0±53.3	<0.001
E2 value on HCG day (pmol/L)	1354.6±1070.3[b,c]	3113.8±1841.0[c]	2209.3±1103.6	<0.001
E2 value on ET day (pmol/L)	803.9±639.1[b,c]	2452.4±1588.1[c]	1463.1±859.5	<0.001
No. of retrieved oocytes	3.7±3.0[b,c]	16.6±8.6[c]	10.0±2.9	<0.001
No. of mature oocytes	3.2±2.4[b,c]	11.8±6.6[c]	7.5±3.0	<0.001
Implantation rate (%)	184 (28.7)[b,c]	246 (49.0)	325 (41.2)	<0.001
Clinic pregnancy rate (%)	155 (24.2)[b,c]	201 (40.0)	289 (36.8)	<0.001
Miscarriage rate (%)	53 (28.8)	60 (24.3)	85 (26.2)	0.588
Live birh rate (%)	101 (15.8)[b,c]	127 (25.4)	185 (23.5)	<0.001

Data presented as mean ± SD or n (%). BMI: Body mass index, AFC: Antral follicle count, FSH: Follicle stimulating hormone, E2: Estradiol, P: Progesterone, HCG: Human chorionic gonadotropin, ET: Embryo transfer

**The total number of miscarriage and live births did not add up to the number of pregnancies as the results of the patients with clinical pregnancy was not obtained.

[a]There was a significant difference with compared group 1 in post-hoc comparison.

[b]There was a significant difference with compared group 2 in post-hoc comparison.

[c]There was a significant difference with compared group 3 in post-hoc comparison.

and live births did not add up to the number of pregnancies because the results of all patients with clinical pregnancy were not obtained.

Table 2 shows the LBR, MCR, IR, and CPR following fresh ET in poor responders (group 1), high ovarian responders (group 2), and normoresponders (group 3) with different E2 declines. In poor responders (group 1), the rate of decrease in the E2 level had no effect on LBR or MCR. In addition, the highest CPR and LBR were in subgroup 1A, which interestingly also had the highest MCR. However, these differences relative to the other subgroups were not statistically significant. In group 2, MCR was highest and LBR lowest in subgroup 2D, whereas IR was lowest in subgroup 2C. In normoresponders (group 3), MCR was significantly higher and LBR significantly lower in subgroup 3D ($p<0.05$) than in subgroups 3A and 3B.

Table 3 shows the clinical features and cycle outcomes of women with high ovarian responses who had a rate of serum estradiol decline of more or less than 60%. High responders were further analyzed according to the ratio of E2 decline in Table 3 (<60% and >60%). The comparison showed that patient age, duration of infertility, basal FSH, P level on hCG day, number of retrieved oocytes, ET, mature oocytes, IR, and CPR were similar ($p>0.05$). However, BMI, AFC, E2 on the day of hCG injection, and MCR were higher in high responders with an E2 decline >60%, whereas LBR was lower. In normoresponders, age, E2 level on hCG injection day, and MR were significantly higher, whereas LBR was significantly lowerin women with an E2 decline >60% (Figure 1).

Table 4 shows the clinical features and cycle outcomes of women with normoresponders (Group 3) who had a rate of serum estradiol decline of more or less than 60%. Patients with a 60% decrease in their E2 levels on the ET day after hCG had a lower LBR and higher MCR, except normoresponders, in whom a similar decline was significant only with respect to MCR (Table 4, Figure 1). In patients with low ovarian reserves, the change in E2 between hCG and ET days had no effect on any clinical variable.

Table 2. Live birth, abortion, implantation and clinical pregnancy rates of fresh embryo transfer cycles in poor responders (Group 1), high ovarian responders (Group 2) and women with normal ovarian responses (Group 3) in subgroups with different E2 declines on the embryo transfer day 3

Groups	No. of patients (%)	Implantation (IPR %)	Clinical pregnancy (CPR %)	Miscarriage (MCR %)	Live birth (LBR %)
Group 1 (n=639)					
Subgroup A (E2%<20)	38 (8.9)	15 (39.4)	15 (39.4)	6 (40)	9 (23.6)
Subgroup B (E2%20-40)	125 (19.5)	33 (26.4)	30 (24.0)	7 (21.2)	23 (18.4)
Subgroup C(E2%41-60)	244 (38.1)	75 (30.7)	62 (25.4)	19 (25.3)	43 (17.6)
Subgroup D (E2%>60)	232 (36.3)	61 (26.2)	48 (20.6)	21 (34.4)	26 (11.2)
P value		0.115	0.086	0.358	0.082
Group 2 (n=502)					
Subgroup A (E2%<20)	119 (23.7)	61 (51.2)	50 (42.0)	8 (13.1)	38 (31.9)
Subgroup B (E2%20-40)	162 (32.3)	94 (58.0)	73 (45.0)	12 (12.7)	52 (32.0)
Subgroup C (E2%41-60)	140 (27.9)	54 (38.5)	45 (32.1)	15 (27.7)	30 (22.4)
Subgroup D (E2%>60)	81 (16.1)	37 (45.6)[$]	33 (40.7)	25 (67.5)[#]	7 (8.6)[*]
P value	0.007[*]	0.135	<0.001[*]		<0.001[*]
Group 3 (n=787)					
Subgroup A (E2%<20)	150 (19.1)	65 (43.3)	60 (40.0)	15 (23.0)	43 (28.6)
Subgroup B (E2%20-40)	228 (29)	90 (39.4)	83 (36.4)	16 (17.7)	64 (28.0)
Subgroup C (E2%41-60)	306 (39)	135 (44.1)	116 (37.9)	37 (27.4)	65 (21.2)
Subgroup D (E2%>60)	103 (12.8)	35 (35)	30 (30)	17 (17)[&]	13 (13)[€]
p		0.362	0.419	0.006*	0.034*

E2: estradiol. Data presented as n (%).
[*]: Significant difference between Subgroup-2-D and Subgroup 2-A and 2-B ($p<0.001$).
[#]: Significant difference between Subgroup 2-D and Subgroup 2-A,2-B and 2-C ($p<0.001$).
[$]: Significant difference between Subgroup 2-D and Subgroup 2-B and 2-C (p:0.007)
[&]: Significant difference between Subgroup 3-D and Subgroup 3-A and 3-B (p:0.011).
[€]: Significant difference between Subgroup 3-D and Subgroup 3-A and 3-B (p:0.014)

Table 3. Clinical features and cycle outcomes of women with high ovarian responses who had a rate of serum estradiol decline of more or less than 60%

	<%60 (n=421)	>%60 (n=81)	p-value
Age (years)	28.7±4.7	30.1±3.8	0.072
*BMI (kg/m^2)	27.4±5.4	29.2±5.0	0.040
Infertilityduration (month)	82.0±52.2	79.6±39.9	0.708
Basal FSH (IU/L)	5.9±1.7	5.5±1.5	0.407
Basal E2 (pmol/L)	43.6±18.5	48.9±15.3	0.006
AFC	22.4±7.2	26.5±5.5	<0.001
E2 value on HCG day (pmol/L)	3013.4±1699.8	4494.3±2256.2	<0.001
P value on HCG day (ng/mL)	1.3±1.3	1.5±1.0	0.391
No. of retrieved oocytes	16.5±7.8	18.7±9.1	0.115
No. of mature oocytes	12.2±6.3	11.8±6.4	0.688
Live birth	121 (28.7)	6 (7.4)	<0.001
Miscarriage	35 (16.7)	25 (67.5)	<0.001
Implantation	209 (49.6)	37 (45.6)	0.513
Clinical pregnancy	168 (39.9)	33 (40.7)	0.888

Data presented as mean ± SD or n (%). BMI: Body mass index, AFC: Antral follicle count, FSH: Follicle stimulating hormone, E2: Estradiol, P: Progesterone, HCG: Human chorionic gonadotropin, ET: Embryo transfer

Table 4. Clinical features and cycle outcomes of women with normo-responders (Group-3) who had a rate of serum estradiol decline of more or less than 60%

	<%60 (n=687)	>%60 (n=100)	p-value
Age (years)	29.2±4.8	31.2±4.5	<0.001
*BMI (kg/m^2)	26.1±4.9	25.6±5.2	0.120
Duration of infertility (month)	66.5±53.6	77.2±57.5	0.106
Basal FSH (IU/L)	6.9±1.6	7.2±1.7	0.060
Basal E2 (pmol/L)	46.8±30.6	50.5±25.9	0.210
AFC	13.0±6.1	12.8±6.3	0.646
E2 on HCG day (pmol/L)	2158.5±1029.4	2627.8±1400.5	<0.001
p on HCG day (ng/mL)	1.0±0.5	1.1±0.6	0.106
No. of retrieved oocytes	10.1±2.9	10.0±3.0	0.744
No.of mature oocytes	7.8±2.9	7.8±3.0	0.971
Live birth	172 (25.1)	13 (13)	0.025
Miscarriage	68 (23.4)	17 (17)	<0.001
Implantation	290 (42.3)	35 (35)	0.105
Clinical pregnancy	259 (37.8)	30 (30)	0.052

Data presented as mean ± SD or n (%). BMI: Body mass index, AFC: Antral follicle count, FSH: Follicle stimulating hormone, E2: Estradiol, P: Progesterone, HCG: Human chorionic gonadotropin, ET: Embryo transfer

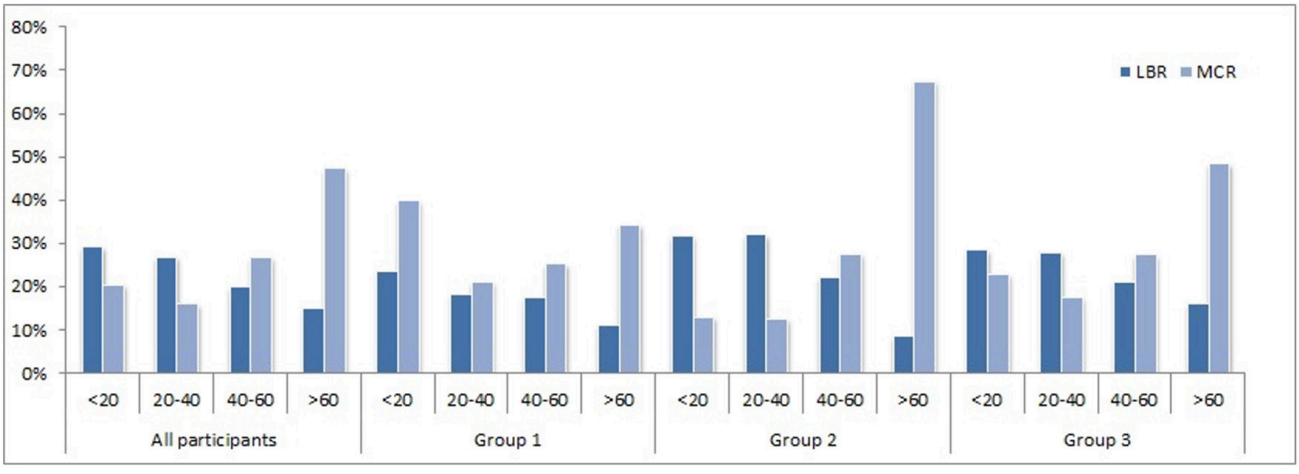

Figure 1. Live birth and miscarriage rates in poor responders (Group 1), high ovarian responders (Group 2) and women with normal ovarian responses (Group 3) in subgroups with different E2 declines on the embryo transfer day 3

Discussion

We found that high ovarian responders who underwent fresh ET cycles with a 60% decrease in their E2 levels on the ET day after HCG had lower live birth rates and higher abortion rates. However, in normoresponder women, this decrease was significant only in abortion rates. In patients with low ovarian reserve, the change in E2 between HCG and the third day ET had no clinical effect.

In our study, the decrease in E2 after the cessation of gonadotropin injection was more prominent in high responders than in low or normal responders. Although this decline in high-responder patients reduces the risk of OHSS, its effect on CPR and LBR is unclear. E2 plays a role in the expression of E2-induced growth factor and E2 receptors[13], and the induction of sufficient P receptors is needed for subsequent P stimulation[12]. Thus, a sudden decrease in E2 may negatively affect implantation[14].

The results of early studies of IVF cycles showed that E2 values measured 24 h after hCG administration are not predictive of reproductive outcome[15,16]. Ozdegirmenci et al.[15] reported a 38% CPR in women with a 30% E2 decline, but in Huang's study[16], the number of women with a 30% decrease was too small to allow a statistical comparison.

The number of patients with an E2 decline >60% was higher in poor responders than in high and normoresponders (36.3% vs. 16.1% and 12.8%, respectively). The subgroup analysis showed that, despite different increments in the E2 decline (subgroup A <20%, subgroup B 20-40%, subgroup C 41-60%, subgroup D >60%), there was no statistically significant difference among the three groups of responders in terms of IR and CPR. However, MCR was significantly higher and LBR significantly lower in subgroup D of the high responders.

An analysis of our patient groups according to the decline in E2 (>60% vs. <60%) showed that high responders with an E2 decline >60% had a lower LBR and higher MCR, whereas IR and CPR did not differ from the corresponding rates in normal and poor responders. In normoresponders with an E2 decline >60%, the E2 level on the day of hCG injection, as well as LBR and MCR, were higher, and the patients were older. While CPR was lower in this group, the difference compared to the other two groups was not statistically significant. We think that the differences in age and BMI may have been a good explanation for the E2 reduction (E2% <20 ~>60%) within the same group. Moreover, the patients' individual cellular response to this mechanical destruction after OPU may also have played a role in this situation.

We also found that the ovarian response and the number of mature oocytes were positively correlated with a favorable IVF outcome. Poor responders with the highest basal E2 level, lowest AFC, and lowest E2 level on the day of hCG injection had the lowest LBR. The main source of post-hCG E2 is the pre-ovulatory E2 produced by oocytes during gonadotropin stimulation. The post-hCG E2 level has been studied for its ability to predict IVF-ET outcome. For example, in an early study by Huang et al.[17], an increase or decrease in the E2 level one day after hCG administration had no effect on the cleavage and fertilization rates of high and low responders.

Few studies have evaluated E2 levels at the beginning of the luteal period. Diluigi et al.[18] divided their patients into two groups according to ovarian responses and then measured E2 values on the day of hCG and 2 days after OPU. After calculating the rates of E2 decline, they found that IR and CPR were lower in high responders with an E2 decline of ≥80%. In our study, we grouped the patients according to their response to ovulation induction and then calculated the percent reduction in E2 levels between the hCG and ET days in each group to analyze the effect of E2 decline rates on the response to gonadotropin therapy. The results showed a significant decline in LBR and an increase in MCR, especially in high and normoresponders, when the E2 decline was >60% (subgroup D). Thus, although the risk of OHSS in these patients is lower due to the sharp decline in serum E2 levels, there is no favorable effect on pregnancy outcome. Whether subgroup D-type patients will benefit from E2 supplementation remains to be investigated.

In our study, we focused on particular groups of patients (poor responders, high responders, and normal responders) in contrast to similar studies on the effect of E2 on ART[12,13]. In addition, our study is one of the few that evaluated E2 levels on the day of ET rather than during the mid-luteal phase. Our results included LBR, which is not reported in most ART studies.

Study Limitations

Our study also has several limitations, especially its retrospective nature and the limited number of patients.

Conclusion

Nonetheless, our findings indicate that the E2 decline on the day of ET may negatively affect ART results in high and normal ovarian responders. Routine measurement of this decline may indicate the need for E2 support alongside P supplementation during the early luteal period. However, larger multicentric studies with prospective designs are needed to definitively determine the relationship of E2 decline with LBR and MCR.

Ethics

Ethics Committee Approval: The study protocol was approved by the hospital ethics committee (Etlik Zubeyde Hanım Research and Training Hospital; no: 90057706-799, date: 19.02.2019).

Informed Consent: Signed informed consent was obtained from all patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Editing assistance: O.A., Technical assistance: B.D., Design: N.N.Y., Data Collection or Processing: R.Ö., Analysis or Interpretation: E.B., Literature Search: N.N.Y., S.D., Writing: N.N.Y., Ö.M.T.

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References

1. Heger A, Sator M, Pietrowski D. Endometrial receptivity and its predictive value for IVF/ICSI-outcome. Geburtshilfe Frauenheilkd 2012;72:710-15.
2. Paulson RJ. Hormonal induction of endometrial receptivity. Fertil Steril 2011;96:530-5.
3. Li M, Yao L, Xin M, Gao M. Dysregulation of collagen expression in peri-implantation endometrium of women with high ovarian response. J Obstet Gynaecol Res 2019;45:1035-44.
4. Fox C, Morin S, Jeong JW, Scott RT Jr, Lessey BA. Local and systemic factors and implantation: what is the evidence? Fertil Steril 2016;105:873-84.
5. Ferraretti AP, La Marca A, Fauser BC, Tarlatzis B, Nargund G, Gianaroli L; ESHRE working group on Poor Ovarian Response Definition. ESHRE consensus on the definition of 'poor response' to ovarian stimulation for in vitro fertilization: the Bologna criteria. Hum Reprod 2011;26:1616-24.
6. Pirtea P, de Ziegler D, Ayoubi JM. Implantation rates of euploid embryos are not influenced by the duration of estradiol priming, but the hormonal environment-estradiol and progesterone-may affect placentation. Fertil Steril 2019;111:1117-8.
7. Kutlu T, Ozkaya E, Ayvaci H, Devranoglu B, Sanverdi I, Sahin Y, et al. Area under curve of temporal estradiol measurements for prediction of the detrimental effect of estrogen exposure on implantation. Int J Gynaecol Obstet 2016;135:168-71.
8. Jirge PR. Poor ovarian reserve. J Hum Reprod Sci 2016;9:63-9.
9. Sharara FI, McClamrock HD. High estradiol levels and high oocyte yield are not detrimental to in vitro fertilization outcome. Fertil Steril 1999;72:401-5.
10. Gardner DK, Weıssman A (Ed). Textbook of assisted reproductive techniques. 5th editon. FL: Boca Raton; 2018.
11. Popovic-Todorovic B, Loft A, Lindhard A, Bangsbøll S, Andersson AM, Andersen AN. A prospective study of predictive factors of ovarian response in 'standard' IVF/ICSI patients treated with recombinant FSH. A suggestion for a recombinant FSH dosage normogram. Hum Reprod 2003;18:781-7.
12. Bai X, Zhang Y, Liu S, Qu D, Su H, Ren H, et al. The decline in serum estradiol on the second day after oocyte retrieval affects the outcome of IVF/ICSI-ET treatment in high ovarian responders. Gynecol Endocrinol 2017;33:452-7.
13. Sonntag B, Loebbecke KC, Nofer JR, Kiesel L, Greb RR. Serum estradiol and progesterone in the mid-luteal phase predict clinical pregnancy outcome in IVF/ICSI cycles. Gynecol Endocrinol 2013;29:700-3.
14. Khalaf Y, Taylor A, Braude P. Low serum estradiol concentrations after five days of controlled ovarian hyperstimulation for in vitro fertilization are associated with poor outcome. Fertil Steril 2000;74:63-6.
15. Ozdegirmenci O, Dilbaz S, Cinar O, Aydin S, Beydilli G, Cakir L, et al. Can serum oestradiol be a predictor of quality of oocytes and embryos, maturation of oocytes and pregnancy rate in ICSI cycles? Gynecol Endocrinol 2011;27:279-85.
16. Huang J, Lu X, Lin J, Wang N, Lyu Q, Gao H, et al. A Higher Estradiol Rise After Dual Trigger in Progestin-Primed Ovarian Stimulation Is Associated With a Lower Oocyte and Mature Oocyte Yield in Normal Responders. Front Endocrinol (Lausanne) 2019;10:696.
17. Huang R, Fang C, Wang N, Li L, Yi Y, Liang X. Serum estradiol level change after human chorionic gonadotropin administration had no correlation with live birth rate in IVF cycles. Eur J Obstet Gynecol Reprod Biol 2014 Jul;178:177-82.
18. Diluigi A, Engmann L, Benadiva C, Maier D, Varhola J, Nulsen J. Serum Estradiol Level on Day of Embryo Transfer Is Associated With Implantation and Pregnancy Rates. Fertil Steril 2005;84:265.