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ORIGINAL ARTICLE / ÖZGÜN ARAŞTIRMA

The impact of pregnancy rates of using two different cut-off levels for high serum estradiol levels on the day of the hCG injection: Results from the same cohort of patients with long down-regulated ART cycles

Aynı YÜT hasta kohortunda hCG günü oluşturulan iki farklı serum östradiol eşik değerlerinin YÜT gebelikleri üzerine etkileri

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ABSTRACT

Objective: To determine, from a single cohort of patients whether on the day of the human chorionic gonadotropin (hCG) injection, two different cut-off levels for high serum estradiol (E2) levels affect pregnancy rates in long-down regulated assisted reproductive technology (ART) cycles.

Patients and Methods: A retrospective cohort analysis was performed in a University affiliated hospital on 539 women undergoing consecutive in vitro fertilization/intacytoplasmic sperm injection (IVF/ICSI) treatment with long-down regulation and recombinant follicular stimulating hormone (FSH) injections. The cut-off level for high E2 concentration was calculated according to a centile analysis of E2 levels on the day of hCG administration. Women in group 1 were divided into subgroup A with E2 levels from the 25th to 75th centiles (1040-2500pg/ml) and subgroup B with E2 levels from the 75th to 100th centiles (>2500pg/ml), respectively. Women in group 2 were divided into subgroup A with E2 levels from the 10th to 90th centile (650-3100pg/ml) and subgroup B with E2 levels from the 90th to 100th centile (>3100pg/ml), respectively. The clinical pregnancy rates and ongoing pregnancy rates were compared.

Results: The clinical pregnancy rates and ongoing pregnancy rates were similar in group 1 and group 2.

Conclusion: High serum E2 levels on the day of the hCG injection day either set at 75th (2500pg/ml) or 90th percentiles (3100pg/ml) do not compromise pregnancy rates in cycles down-regulated with gonadotropin-releasing hormone (GnRH) analogues.

Key words: Gonadotropin-releasing analogue, Human chorionic gonadotropin, Pregnancy, long analogue cycle, Estradiol

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ÖZET

Amaç: Yardımcı üreme teknikleri (YÜT) uygulanan hasta kohortunda insan koriyonik gonadotropin (hCG) günü oluşturulan iki farklı serum östradiol (E2) eşik değerlerinin YÜT gebelikleri üzerine etkilerinin araştırılması.

Hastalar ve Yöntem: Üniversiteye bağlı eğitim hastanesinde uzun süreli gonadotropin salgılayıcı hormon baskısından sonra kullanılan rekombinant folikül stimüle edici hormon (FSH) ile YÜT tedavisi alan 539 ardışık kadın retrospektif analize alınmıştır. hCG günü alınan serum E2 seviyesinin yüksek eşik değeri persentil analizine göre yapılmıştır. Grup 1 için serum E2 seviyeleri 25–75inci persentilde (1040-2500pg/ml)olanlar alt grup A ; serum E2 seviyeleri 75–100üncü persentilde (>2500pg/ml)olanlar alt grup B olarak ayrılmıştır. Grup 2 için serum E2 seviyeleri 10–90ıncı persentilde olanlar(650-3100pg/ml) alt grup A ve serum E2 seviyeleri 90–100üncü persentilde (>3100pg/ml)olanlar alt grup B olarak ayrılmıştır. Klinik ve devam eden gebelik oranları karşılaştırılmıştır.

Bulgular: Hem grup 1'de hem de grup 2'de klinik ve gebelik oranları benzerdir.

Sonuç: hCG günü serum E2 seviyelerinin eşik değeri 75inci (2500pg/ml), veya 90ıncı persentil (3100pg/ml) üzerinde olması GnRH analogları ile baskılanmış uzun protokol YÜT sikluslarında gebelik oranlarını olumsuz etkilememektedir.

Anahtar kelimeler: Gonadotropin salgılayıcı hormon analogu, İnsan korionik gonadotropin, Gebelik, Uzun analog siklusu, Östradiol

Introduction

There is dispute about the impact that elevated estradiol (E2) levels (or a high number of retrieved oocytes) at the time of human chorionic gonadotropin (hCG) administration may have on pregnancy for a subgroup of higher responder patients having in vitro fertilization (IVF) treatments. Studies showing either no adverse effects or appalling pregnancy rates (PRs) of high serum E2 levels have been published [1-5]. It has been suggested that increased ovarian steroid hormone secretion from controlled ovarian hyperstimulation (COH)

may compromise endometrial receptivity for embryo implantation [6,7]. However, conflicting reports exist concerning the impact of COH on pregnancy rates after IVF-embryo transfers (ET) [8–10]. Simon et al [3] and Yu Ng et al [11] reported reduced pregnancy rates, while Chenette [12] and Gelety and Buyalos [13] found that higher clinical pregnancies were obtained from IVF cycles with high E2 levels. High responders have been defined variously as patients who had peak E2 level of > 3000 pg/ml(conversion factor of 3.671), > 15 retrieved oocytes or > 10 retrieved oocytes [11].

Although implantation results from good quality embryos, this is not the only factor contributing to successful implantation, because the maternal endometrium is at least of equal relevance. In IVF, the main reason for the low implantation results is that the quality of the endometrial factor is affected during pharmacological treatments (hormonal therapy (HT) and COH), and this can be proven when comparing implantation and pregnancy rates in normal cycles versus IVF and oocyte donation recipients [14]. As the aim of ovulation induction is to recruit more oocytes, and subsequently more good quality embryos, supraphysiological concentrations of steroid hormones (oestradiol and progesterone) are produced that may affect endometrial receptivity [15]. Altered regulation of steroid receptor expression in the human endometrium could be implicated since a significant reduction in nuclear receptors for progesterone and E2 in both the glands and stroma, has been demonstrated in COH cycles [16].

Arbitrary threshold E2 levels on the day of hCG administration have been used to create groups of patients for comparison, but also percentile analysis of E2 levels have been used. Studies suggesting that there is a positive or a negative association between E2 levels and the chance of pregnancy failed to concur on a threshold level of E2 at which the probability of pregnancy is significantly altered. We aimed to determine whether two different cut-off values for high serum E2 levels on the day of the hCG injection in the same cohort of patients affect pregnancy rates in long-down regulated ART cycles.

Patients and Methods

Five hundred and thirty-nine consecutive women undergoing IVF/ICSI cycles at the ART unit in a university affliated hospital, formed the cohort of patients from which two study groups were constructed. In none of these patients had the cycles were been cancelled. In study group 1 the women were placed into two subgroups according to a centile analysis of E2 levels on the day of the hCG administration, the subgroups being from the 25th to 75th percentile and from 75th to 100th percentile, where 2500 pg/ml was the cut-off point. Study group 2 consisted of women divided into two subgroups on the basis of E2 levels on the day of hCG administration from the 10th to 90th percentile and from the 90th to 100th percentile, where 3100 pg/ml was the cut-off point. The data from patients in the lower 25th percentile in group 1 and lower 10th percentile in group 2 were excluded. All practices and protocols conformed to the ethical requirements for ART programs of the Ethics Commitee of the institution and conformed with the provisions of the Declaration of Helsinki.

All patients underwent ovarian stimulation with gonadotropins and gonadotropin releasing hormone (GnRH)-agonist for pituitary down-regulation. For long protocols, pituitary desensitisation was achieved by s.c. administration of leuprolide acetate during the luteal phase of the preceding cycle before the start of gonadotropin stimulation. COH was accomplished with s.c. administration of recombinant FSH (Follitropin alpha; Serono). The initial standard gonadotropin dose was 225 IU recFSH for normo-responders. If age was over 35, starting gonadotropin dose 300IU was considered. Ten thousand IU of human chorionic gonadotropin (hCG, 10,000 IU Profasi, Serono) was administered when at least one follicle had a mean diameter of 18 mm. Transvaginal oocyte retrieval was performed 35 or 36 h after hCG injection. The scoring system used for the selection of embryos to transfer at cleavage stage was previously described [17]. Implantation, clinical pregnancy rates and ongoing pregnancy rates were compared between the groups.

Statistical Evaluation

All analyses used StataSE 10.0 software (Statacorp, Texas, USA). Statistical analysis was by Student's t-test on mean values and by the chi-square test on outcome rates related to pregnancy outcomes ; $p<0.05$ was considered significant.

Results

There were 264 women in subgroup A and 147 in subgroup B of group 1. 128 patients who had E2 levels below the 25th percentile on the day of hCG administration were excluded. The mean age, serum level of FSH on cycle day 3 and the body mass index (BMI) were similar between groups. Indications for ART in subgroup A were male factor (36.9%), tubal (19.2%), minimal endometriosis (9.4%), polycystic ovary syndrome (PCOS) (6.3%) or unexplained infertility (31%). The corresponding percentages in sugroup B were 34.5%, 28.2%, 8.5%, 7% and 24.6%, respectively. The duration of gonadotropin stimulation and the total dose of FSH used were alike in subgroups A and B. The mean number of eggs collected and the mean number of mature and fertilized oocytes were higher in subgroup B. On day 3, the mean number of embryos with more than 6 cells were higher in subgroup B than in subgroup A. However, the average scores of transfered embryos were comparable in subgroups A and B (Table I).

Table I. The patient demographics and cycle characteristics of the study groups

	Group 1			Group 2		
	Subgroup A (n=264)	**Subgroup B (n=147)**	**P value**	**Subgroup A (n=411)**	**Subgroup B (n=56)**	**P value**
Age (years)	33.94± 4.30	33.70 ± 4.63	0.60	33.99± 4.32	34.07 ± 4.77	0.90
Body mass index (kg/m2)	26.15± 7.43	25.81± 6.34	0.68	26.34 ± 7.39	25.33 ± 6.34	0.36
Cycle day 3 FSH (mIU/ml)	6.09± 2.14	5.75 ± 1.98	0.12	6.22 ± 2.29	5.60 ± 2.03	0.06
Duration of stimulation with gonadotropin (days)	9.49± 1.45	9.52 ± 1.32	0.84	9.49± 1.56	9.45 ± 1.23	0.86
Duration of GnRH analogue (days)	29.03± 6.54	27.63± 3.95	0.02	28.82 ± 5.94	26.97 ± 3.72	0.02
Total dose of FSH used (IU)	2792.33± 1022.35	2611.74± 972.54	0.08	2828.37± 1108.05	2545± 950.58	0.06
E2 level on the day before hCG day (pg/ml)	1213.62± 381.50	2038.65± 525.43	0.0001	1243.67± 525.40	2254.38± 637.32	0.0001
E2 level on hCG day (pg/ml)	1697.23± 432.43	3090.63± 490.25	0.0001	1762.31± 699.99	3572.87± 439.97	0.0001
E2 level per oocyte retrieved (pg/ml)	163.48± 97.65	181.76 ± 67.83	0.054	165.68± 89.53	182.18 ± 75.02	0.21
Number of aspirated oocytes per retrieval	12.45± 5.47	19.11± 7.83	0.0001	12.35± 6.08	22.07± 9.45	0.0001
Number of inseminated oocytes per retrieval	11.33± 5.24	17.46± 8.14	0.0001	11.14 ± 5.70	21.21± 9.62	0.0001
Number of fertilized oocytes per retrieval	7.98± 4.73	12.02± 7.22	0.0001	7.79± 4.98	14.82± 8.23	0.0001
Number of embryos transferred on day 3	3.30± 0.86	3.29± 0.85	0.91	3.32± 0.84	3.43± 0.91	0.44
Average WIH score of embryos transfered on day 3 *	6.61± 1.17	6.58± 1.33	0.81	6.55± 1.21	6.73± 1.24	0.36

All values are given as mean and standard deviation (SD)
P< 0.05 is statistically significant
* The sum of "development+ fragmentation+symmetry"of each embryo transferred divided by number

Table II. Pregnancy outcomes

	Group 1			Group 2		
	Subgroup A (n=264)	**Subgroup B (n=147)**	**P value**	**Subgroup A (n=411)**	**Subgroup B (n=56)**	**P value**
Implantation rate per transfer	22.34± 0.31	21.42±0.28	0.79	20.74± 0.29	23.29± 0.30	0.60
Average WIH score* of transferred embryos that resulted in clinical pregnancy	7.02 ± 0.99	6.88 ± 1.17	0.39	6.92 ± 1.06	7.02 ± 1.00	0.68
Clinical pregnancy per day 3 transfer	125 (49.80%)	79 (58.09%)	0.12	210 (51.85%)	32 (59.26%)	0.31
Average WIH score* of transferred embryos that resulted in ongoing pregnancy	7.08 ± 1.00	6.95 ± 1.08	0.49	6.98 ± 1.07	6.98 ± 0.77	0.99
Ongoing pregnancy per day 3 transfer	107 (43.27%)	67 (49.63%)	0.23	176 (43.86%)	25 (47.17%)	0.65

WIH scores are given as mean and standard deviation (SD)
Pregnancy outcomes are given as number, and percentage (%) in parentheses
P< 0.05 is statistically significant
* The sum of "development+ fragmentation+symmetry"of each embryo transfered divided by number

There were 411 women in subgroup A and 56 in subgroup B of group 2. Seventy two patients who had E2 levels below the 10th percentile on the day of hCG administration were excluded. The mean age , serum level of FSH on cycle day 3 and BMI were similar between groups. Indications for ART in subgroup A were male factor (36.2%), tubal (21.3%), minimal endometriosis (9%), PCOS (6.4%) or unexplained infertility (29.8%). The corresponding percentages of distribution in subgroup B were 31.6%, 33.3%, 12.3%, 5.3% and 19.3%, respectively. The duration of gonadotropin stimulation and the total dose of FSH used were alike in subgroups A and B. Just as the mean serum E2 levels on the day of hCG administration were higher in subgroup B so were the mean number of eggs collected and the mean number of mature and fertilized oocytes were higher. On day 3, the mean number of embryos with more than 6 cells were more in subgroup B than in subgroup A. However, the average score of transfered embryos were comparable in subgroups A and B (Table I).

The mean clinical pregnancy rates per cleavage stage transfer were alike between the subgroups of groups 1 and 2. Similarly, the ongoing pregnancy rates per cleavage stage transfer were almost the same for the subgroups of groups A and B (Table II).

Discussion

In most reports where groups of patients were used for comparisons, the groups were created by arbitrary threshold E2 levels on the day of hCG administration. Interval increments of one thousand or five hundred, and also percentile analysis of E2 levels have been used [18]. We have compared the fresh ET results in long down - regulated ART cycles. We grouped our cohort of infertile women according to a centile analysis of E2 levels on the day of hCG administration. Two cut-off points were chosen for high E2 levels: 75 percentile and 90 percentile. In the literature differences in the type of analogue or in the analogue protocol used and in the day on which the embryo transfer took place, have affected the observed results so that they vary from one another. We have included ART cycles where only recombinant FSH was used for COH after long down-regulation with GnRH analogue used for COH. Criteria used for triggering the final oocyte maturation were based solely on follicular diameters. The hCG was administered as soon as a threshold of follicular development was reached, regardless of E2 levels [19,20].

Supraphysiological levels of E2 during IVF-ET cycles have been incriminated as having a detrimental effect on endometrial receptivity and pregnancy [3-11-14-21,22]. On the contrary, increased pregnancy rates have been proposed by other studies [12, 13]. Chenette et al. [12] grouped 216 patients in three groups according to E2 levels on the day of hCG administration (<1722, 1722–2777, >2777 pg/ml) and noted that significantly higher clinical pregnancy rates per oocyte retrieval were observed in the highest E2 group compared with the other groups. Gelety and Buyalos [13] compared 25 patients undergoing IVF who had E2 levels on the day of hCG >5000 pg/ml with 25 patients in whom E2 levels were <3500 pg/ml (control group). The control group was matched for age, duration and type of infertility, and stimulation protocol. A higher clinical pregnancy rate per embryo transfer was observed in the high E2 group. More embryos were transferred in the high compared with the low E2 group, although the difference was marginally significant.

Embryo quality and endometrial receptivity have been identified as important determinants of reproductive outcome in assisted reproduction [14-23]. In our study embryos were transferred at the cleavage stage. Average embryo scores were comparable between the subgroups. Decreased implantation rates have been claimed when the developing endometrium was exposed to the effects of COH [8-21,22]. In contrast to previous reports, [9-21,22] we observed similar clinical and ongoing pregnancy rates between the subgroups in both study groups.

Simon et al. [3] divided patients into eight groups according to E2 levels on the day of hCG administration using 500 pg/ml increments (from 500 to >3500 pg/ml). A significantly lower pregnancy rate per cycle started was observed in the groups of patients with higher E2 levels (E2 >2500 pg/ml) compared with those with lower E2 levels (E2 <2500 pg/ml). Ng et al. [11] divided patients into three groups according to E2 levels on the day of hCG administration (<10.000, 10.000–20.000, >20.000 pmol/l). A significantly lower clinical pregnancy rate per embryo transfer was observed in the group of patients with E2 levels >20.000 pmol/l compared with those with E2 levels between 10.000 and 20.000 pmol/l. Similar numbers of embryos were transferred in the groups compared.

Toner et al.[4] found that despite a slight decrease in fertilization rates in those cycles with > 10 retrieved oocytes, pregnancy rates were not different between the groups. In our study subgroups with E2 concentrations more than the cut-off level, there were more fertilized oocytes than the subgroups with lower E2 levels. Just as Tarin et al [24] showed no difference in pregnancy rates between low-to-moderate and high responders so we observed no difference in either the clinical or the ongoing pregnancy rates between the subgroups . We observed that with high estradiol levels more surplus embryos are likely to be available for cryopreservation and used for later cryo-ETs. The presence of embryos suitable for freezing suggested that the embryo quality was not affected in a negative way.

Contrary to studies showing either negative or positive associations of pregnancy with high levels of E2 on the day of hCG administration there are reports confirming that high E2 levels did do not appear to adversely affect embryo quality and consequent pregnancy rates [5]. Sharara and McClamrock [25] analysed 106 patients in four groups according to E2 levels on the day of hCG administration, using thousand interval increments (<2000, 2000–3000, 3000–4000, >4000 pg/ml). Papageorgiou et al. [26] divided 762 patients into three groups according to a centile analysis of E2 levels on the day of hCG administration (0–10th centile, 10th –90th centile, 90th – 100th centile). Chen et al. [27] used centile analysis to divide 697 patients in three groups according to E2 levels on day of hCG administration (<1289, 1289–2495, >2495 pg/ml). In agreement with these studies we have found that clinical pregnancy rates per embryo transfer were similar between our study subgroups no matter which cut-off level was chosen for the high E2 level.

We have investigated for the first time where two cut-off levels for high E2 level were formed in the same cohort of patients and pregnancy outcomes were analysed. Cut-off levels set either at the 75th percentile or 90th percentile will not compromise pregnancy rates. Hence, each ART program must consider their distribution of E2 on the day of hCG administration and establish their line of action accordingly. Since high E2 levels on the day of hCG administration did not seem to adversely affect pregnancy rates, serum E2 surveillance should be offered only in some subset of cycles where the risk of ovarian hyperstimulation syndrome is high.

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