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Comparison of the luteal phase estradiol priming stimulation and standard antagonist protocols in patients with diminished ovarian reserve undergoing ICSI

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The study protocol was approved by the Etlik Zubeyde Hanim Women's Health Training and Research Hospital Local Ethics Committee (2019/209).
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Abstract

Background/Aim: No consensus on the optimal stimulation protocol for increasing *in vitro* fertilization (IVF) treatment's success rate in patients with diminished ovarian reserve is available. This study aimed to compare IVF outcomes in patients with diminished ovarian reserve (DOR) stimulated with a luteal phase estradiol (E2) priming protocol versus the standard antagonist protocol.
Methods: This retrospective cohort study included 603 patients who underwent intracytoplasmic sperm injection cycles (ICSI) after the diagnosis of DOR and who were stimulated with the luteal E2 priming protocol (E2 priming group; n = 181) or the standard antagonist protocol (antagonist group; n = 422). Groups were compared in terms of demographic characteristics, ovarian stimulation results, ICSI cycle outcomes, clinical pregnancy, and live birth rates per embryo transfer.
Results: The duration of ovarian stimulation was longer, and the total gonadotropin dose used was significantly higher (P = 0.001) in the E2 priming group than in the antagonist group. The number of embryos transferred was higher in the antagonist group when compared with E2 priming group (0.87 (0.75) versus 0.64 (0.49); P = 0.01), but no statistically significant difference in terms of embryo quality between groups was found (P > 0.05). The cycle cancellation rate, clinical pregnancy, and live birth rates per embryo transfer were similar in both groups.
Conclusions: No difference between IVF outcomes in the patients diagnosed with DOR who were stimulated with the antagonist protocol and the luteal E2 priming protocol was detected. The antagonist protocol might be considered more advantageous because of the shorter treatment duration and lower doses of gonadotropin. This protocol also allows more embryos to be transferred. Additional randomized controlled trials are needed to verify these findings.

Keywords: Luteal phase estradiol priming, Antagonist protocol, Diminished ovarian reserve, Intracytoplasmic sperm injection

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Introduction

Diminished ovarian reserve (DOR) refers to the patients with decreased number and quality of oocytes. The number of patients with the diagnosis of DOR who present for *in vitro* fertilization (IVF) and intracytoplasmic sperm injection (ICSI) treatment cycles with the has increased markedly in recent years. No standard definition for DOR has been put forth to date, and the incidence among IVF patients is reported to be 10% [1, 2]. A decrease in antral follicle count, decrease in number of oocytes retrieved, higher cycle cancellation rates, and lower fertilization, implantation, clinical pregnancy, and live birth rates are still significant problems in DOR patients.

Controlled ovarian hyperstimulation (COS) is essential for multi-follicular development and is the main step in the IVF protocol. The optimal number of retrieved oocytes is important for development of an increased number of embryos available for transfer and higher pregnancy rates in IVF cycles [3]. The most appropriate ovarian hyperstimulation protocol for DOR patients is controversial [4]. Several strategies are recommended for IVF patients with DOR to increase the outcomes. These strategies include increasing the gonadotropin dose administered during controlled ovarian stimulation [5], using multiple types of gonadotropins, estradiol priming [6], antagonist protocol, and alternative supplementation of dehydroepiandrosterone (DHEA), growth hormone [7] and oral L-arginine [8]. Nonetheless, no consensus on the optimal stimulation method for increasing IVF treatment's success rate in DOR patients has been reached [9].

The present study aimed to compare the IVF outcomes (the number of retrieved oocytes, cycle cancellation and clinical pregnancy rates, live birth rate per embryo transferred in DOR patients treated with the standard antagonist protocol and the luteal estradiol (E2) priming protocol).

Materials and methods

This retrospective study included 603 DOR patients who underwent ICSI treatment cycles according to the standard antagonist (antagonist group) and luteal E2 priming antagonist protocols (E2 priming group) between January 2007 and July 2019. A total of 5236 patients were treated during this period at the Etlik Zubeyde Hanim Women's Health Training and Research Hospital's IVF center. The electronic records from 753 patients diagnosed with DOR were screened. After excluding patients who underwent different treatment protocols and who had insufficient medical records, 603 patients were examined.

The study protocol was approved by the Etlik Zubeyde Hanim Women's Health Training and Research Hospital Local Ethics Committee (2019/209). In reproductive period, FSH level < 12 IU/L and E2 level < 80 pg/ml are considered as normal levels of these hormones. Patients with at least two of three criteria were considered to have DOR: 1) basal serum follicle-stimulating hormone (FSH) level ≥ 12 IU/L and E2 level > 80 pg/ml measured within the last three months of the IVF cycle, 2) antral follicle count (AFC) < 7.3, and/or (3) serum Antimullerian hormone (AMH) level < 1.1 ng/ml measured over six months. Several factors, including infertility, indication for pre-implantation genetic diagnosis (PGD), freeze–thawed embryo cycles, presence of chromosomal and/or autoimmune disorders, and/or endocrine or metabolic disorders (such as diabetes, hypo/hyperthyroidism, and hyperprolactinemia) were considered exclusion criteria.

Demographic characteristics, such as age, body mass index (BMI), number of previous IVF cycles, duration of infertility, and basal characteristics (AFC, AMH measurement, and serum basal FSH, E2, and luteinizing hormone (LH) levels) were recorded. Groups were compared in terms of duration of ovulation induction, total gonadotropin dose used, E2 and progesterone (P) levels, and endometrial thickness on hCG (conception) day, the number of retrieved oocytes, mature oocytes, and fertilized oocytes. The number of embryos (good or poor quality) transferred, E2 and P levels, and endometrial thickness on the transfer day were also analyzed. The number of embryo transfer (ET) cycles, the number of canceled cycles, day of embryo transfer (day 3 or 5), biochemical pregnancy, clinical pregnancy, and live birth rates per ET were compared between the groups.

Antagonist protocol

In the standard flexible GnRH antagonist protocol, gonadotropin was initiated on day 3 of the menstrual cycle. The patients received gonadotropin at a starting dose of 225 to 450 IU/day using recombinant FSH (recFSH; Gonal-F, Merck-Serono, Istanbul, Turkey or Puregon; Organon, Istanbul, Turkey) with human menopausal gonadotropin (hMG; Menagon; Ferring, Istanbul, Turkey or Merional; IBSA, Istanbul, Turkey). The dose was determined based on age, BMI, and AFC and tailored according to follicular development. When the mean diameter of ≥ two follicles reached 13–14 mm during stimulation, the antagonist was initiated (Cetrotide, Merk-Serono, Istanbul, Turkey) and was continued until the day of recombinant human chorionic gonadotrophin (rechCG) administration.

Luteal phase estradiol priming protocol

The patients in the luteal E2 priming protocol group received oral E2 hemihydrate (Estrofem, Novo-Nordisk, Istanbul, Turkey) twice a day, beginning on day 21 of the previous cycle until the first day of menses. The gonadotropins (recFSH and hMG) were initiated on day 3 of menstruation similar to the standard antagonist protocol and when ≥ two follicles reached 13–14 mm in diameter, the antagonist, Cetrotide, was initiated and continued until the day of rechCG administration.

Ovarian response was monitored by serial transvaginal ultrasound and serum estradiol and LH assessments. Rec hCG of 250 mg (Ovitrelle, Merck-Serono, Poland) was administered to all subjects for the final oocyte maturation when at least three follicles reached a diameter of 18 mm. Transvaginal oocyte retrieval (OPU) was performed 35.5–36 hours after hCG administration, and intracytoplasmic sperm injection (ICSI) was performed for all mature oocytes. The presence of two pronuclei 18–20 hours following ICSI confirmed fertilization. The absence of fertilization was defined as total fertilization failure (TFF). Embryo development was assessed daily, and a development arrest for 24 h or the presence of an embryo with degenerated or lysed cells was accepted as embryo development arrest (EDA). For assessment of embryonic quality, embryos were graded using an embryo scoring system as described by Baczkowski et al. [10].

Cycle cancellation was classified as no follicular development with ovarian hyperstimulation, no oocytes retrieved in OPU, and/or presence of TFF and EDA.

Embryo transfer was performed on either day 3 or 5 under ultrasonography guidance. Luteal phase support was provided to all patients with the combination of intramuscular (Progestan amp, Koçak Farma, Turkey) and vaginal progesterone (Crinone 8% gel, Merck-Serono, UK). A positive pregnancy test was diagnosed by blood β-hCG levels obtained 14 days after OPU. Clinical pregnancy was defined by the presence of an intrauterine gestational sac with detectable fetal cardiac activity as assessed by transvaginal ultrasonography. Spontaneous abortion was defined as the loss of a nonviable fetus/pregnancy up to 20 weeks. Live birth was defined as the delivery of a viable fetus after 24 weeks of gestation.

The primary outcomes were clinical pregnancy rate per ET, live birth rate per ET, and the cycle cancellation rate. The secondary outcomes were the number of retrieved oocytes, mature oocytes and the number of embryos transferred.

Statistical analysis

Statistical analyses were performed using the SPSS Windows version 23.0 (SPSS Inc., Chicago, IL). The distribution of the continuous variables, coefficients of skewness, and kurtosis were checked using the Kolmogorov–Smirnov test and histograms. Continuous variables were defined as mean (standard deviation (SD)), and categorical variables were defined as frequencies and numbers (%). The Mann–Whitney U test was used to evaluate comparison between non-normally distributed continuous variables and two-level variables. The chi-squared test was used to evaluate categorical variables. A value of $P < 0.05$ was accepted as statistically significant.

Results

A total of 603 patients (422 (70.0%) stimulated with the standard antagonist protocol, and 181 (30.0%) stimulated with luteal E2 antagonist protocol) were included. Mean age, duration of infertility, number of IVF cycles, basal FSH, LH, and E2 levels, and AFC did not differ significantly between the two protocol groups ($P > 0.05$) as shown in Table 1. The BMI of patients who were stimulated with the standard antagonist protocol was significantly higher than in patients who were stimulated with luteal E2 antagonist protocol ($P = 0.02$). Serum AMH levels were higher in the antagonist group than in the E2 priming group [0.53 (0.22) versus 0.26 (0.06)] ($P = 0.001$) as shown in Table 1.

Duration of ovulation induction was significantly longer in the E2 priming group versus the standard antagonist group [9.7 (2.2) versus 9.2 (2.0) days; $P = 0.001$]. The total gonadotropin dose was also significantly higher in the E2 priming group [3141.76 (948.06) IU versus 2734.66 (1038.49) IU; $P = 0.001$]. Serum E2 and P levels on hCG day, endometrial thickness on hCG day, and the number of retrieved oocytes, mature oocytes, fertilized oocytes did not differ significantly between these two groups ($P > 0.05$). The number of embryos transferred was higher in the antagonist group than the E2 priming group [0.87 (0.75), 0.64 (0.49)], but the number of good or poor-quality embryos that were transferred did not differ between the groups ($P > 0.05$). Serum E2 levels on transfer day was lower, whereas serum P levels and the endometrial thickness on transfer day was higher in the E2 priming group compared with the antagonist group ($P > 0.05$).

The rate of embryo transfer cycles (53.1% versus 47.5%) and the cycle cancellation rate (46.9% versus 52.5%) didn't differ between the groups (Table 2). Day of ET, biochemical pregnancy rate per ET (6.3% versus 10.7%), clinical pregnancy rate per ET (31.5% versus 25%), spontaneous abortion rate per ET (12.1% versus 10.5%), and live birth rate per ET (19.2% versus 14%) also did not differ between groups ($P < 0.05$) as shown in Table 2.

Table 1: Demographic characteristics and COS parameters of patients stimulated with antagonist protocol and luteal E2 antagonist protocol

	Antagonist group n = 422	E2 priming group n = 181	*P*-value
Maternal age, years	35.20 (5.24)	35.34 (4.89)	0.865
Body mass index, kg/m^2	26.90 (4.71)	25.60 (4.83)	0.002
Duration of infertility, months	63.9 (56.1)	59.9 (56.3)	0.291
Number of IVF cycle	1.84 (1.26)	1.85 (1.28)	0.951
Basal FSH level, IU/L	11.77 (6.98)	12.97 (7.26)	0.012
Basal LH level, IU/L	5.52 (2.98)	5.68 (4.00)	0.941
Basal E2 level, pg/ml	51.33 (48.80)	52.30 (34.41)	0.321
AMH, ng/ml	0.53 (0.22)	0.26 (0.06)	0.001
Antral follicul count	5.27 (3.03)	5.09 (3.01)	0.315
Cos Parameters			
Duration of ovulation induction, days	9.21 (2.05)	9.71 (2.20)	0.001
Total gonadotrophin dose, IU	2734.66 (1038.49)	3141.76 (948.06)	0.001
E2 level on hCG day, pg/ml	1029.61 (581.70)	1040.32 (560.98)	0.008
P level on hCG day, ng/ml	0.59 (0.60)	0.75 (0.24)	0.001
The endometrial thickness on hCG day, mm	9.37 (1.64)	9.41 (1.50)	0.213
Number of retrieved oocytes	4.40 (2.51)	4.33 (2.54)	0.941
Number of mature oocytes	3.30 (2.04)	3.14 (1.95)	0.566
Number of fertilized oocytes	1.57 (1.53)	1.77 (1.49)	0.378
Number of embryos transferred	0.87 (0.75)	0.64 (0.49)	0.001
Good quality	1.05 (0.52)	1.06 (0.38)	0.683
Poor quality	0.17 (0.41)	0.14 (0.36)	0.522
E2 level on transfer day, pg/ml	584.94 (310.18)	507.28 (232.13)	0.001
P level on transfer day, ng/ml	42.82 (14.76)	50.81 (15.35)	0.001
The endometrial thickness on transfer day	9.90 (1.78)	10.15 (1.26)	0.001

FSH: follicle-stimulating hormone, LH: luteinizing hormone, E2: Estradiol, P: Progesterone, AMH: antimullerian hormone, COS: Controlled ovarian stimulation, hCG: human chorionic gonadotrophin, IVF: *In vitro* fertilization. Data are presented as mean (SD).

Table 2: IVF outcomes of patients stimulated with antagonist protocol and luteal E2 antagonist protocol

	Antagonist group n = 422	E2 priming group n = 181	*P*-value
Number of embryo transferred cycles	224 (53.1)	86 (47.5)	0.210
Number of canceled cycles	198 (46.9)	95 (52.5)	0.870
No folliculer development	41 (21.1)	21 (21.3)	
No oocytes in OPU	32 (16.1)	12 (12.8)	
TFF	52 (26.1)	24 (25.5)	
EDA	73 (36.7)	38 (40.4)	
Day of ET			0.130
Day 3	180 (80.7)	75 (87.2)	
Day 5	44 (19.6)	11 (12.8)	
IVF outcome per ET			0.287
Biochemical pregnancy	14 (6.3)	9 (10.7)	
Clinical pregnancy	70 (31.5)	21 (25)	
Pregnancy outcome per ET			0.725
Spontaneous abortion	27 (12.1)	9 (10.5)	
Live birth	43 (19.2)	12 (14)	

OPU: oocyte pick up, TFF: total fertilization failure, EDA: embryo development arrest, ET: embryo transfer, IVF: *In vitro* fertilization. Data are presented as n (%).

Discussion

The present study compared the standard antagonist and luteal E2 priming protocols in terms of IVF outcomes in DOR patients. Although ovulation induction duration and the total gonadotropin dose were significantly higher in the E2 priming group, cycle cancellation, and clinical pregnancy, and live birth rates per ET were similar in both stimulation groups.

The definition of DOR varies across studies [11–13]. Baseline FSH, AMH, and AFC were recently used to predict the ovarian reserve [14], and the present study used these four parameters to define DOR (baseline values for FSH, E2, AMH, and AFC).

Many different methods are used to treat DOR, but no one method is better than another one [9]. The use of the combined E2 priming and antagonist protocols was first described by Dragisic et al. [15]. Studies have shown that E2 administration during the luteal phase of the previous cycle causes suppression of the early elevation of FSH and results in homogenous growth in early antral follicles preventing follicular asynchrony [16,17]. Additionally, lower cycle cancellation rates, higher number of ETs, and higher pregnancy rates were noted in patients treated with the luteal E2 priming protocol [18,19]. Oral estradiol valerate, transdermal estradiol hemihydrate patches, and an estradiol pump were used for E2 priming and when compared to the other groups, it was stated that pregnancy rates were not different between the three groups [20].

Most of the studies comparing the luteal E2 priming protocol with the standard antagonist protocol have been published in poor ovarian response (POR) patients [6, 21, 22]. In two of these studies, the total gonadotropin dose administered during stimulation was found to be significantly higher in patients in the E2 priming protocol arm [21, 22] than in the other arms. Another study reported that no difference was found in the total gonadotropin dose between the E2 priming and antagonist protocol groups [6]. In the present study, the total gonadotropin dose was significantly higher in the E2 priming protocol group.

Mutlu et al. [21] compared the luteal E2 priming and the standard antagonist protocols, reporting that the number of oocytes retrieved, the number of mature oocytes, and the number of embryos transferred did not differ significantly between the groups. A retrospective study that included 86 patients who had been primed with oral E2 valerate and the antagonist protocol observed that the number of oocytes retrieved, the number of fertilized oocytes, and the percentage of good quality embryos were higher in the E2 priming group [6]. More recently, Lee et al. [22] compared the IVF outcomes in 65 POR patients treated with luteal oral E2 valerate and the antagonist protocol, noting that the number of oocytes retrieved and the number of mature oocytes in the E2 priming protocol group were significantly higher than in the antagonist group. The number of retrieved, mature, and fertilized oocytes did not differ between groups in the present study.

Chang et al. [6] reported that the pregnancy rate per ET was higher, and the cycle cancellation rate was significantly lower in the E2 priming protocol group than in the antagonist protocol group in poor responders. Lee et al. [22] reported that clinical pregnancy and live birth rates were significantly higher in the E2 priming group than in the antagonist group. In contrast, Mutlu et al. [21] noted that the clinical pregnancy rate and the live birth rate per ET did not differ between the luteal E2 priming and antagonist protocol groups. They also observed that no significant differences between the cycle cancellation rates between the two protocols existed, similar to the results in the present study. Recently, the luteal E2 priming protocol with the small number of patients with 4 mg oral E2 was prospectively compared with standard antagonist group, and no difference in IVF outcomes was noted [23]. One retrospective observational study was published in the literature that compared luteal E2 priming using E2 hemihydrate and antagonist protocol groups in normo-responders and poor responders. In normo-responders, no difference between the groups in terms of IVF outcomes was found. However, in the poor responder group, pregnancy and live birth rates per ET were higher in the luteal E2 priming group [24]. The heterogeneity of the findings might be due to the small number of relevant studies, differences in the type of estradiol administered, and/or small patient populations.

Limitations

The limitation of the present study is the retrospective design; however, its strength is the sizeable number of patients included in the study.

Conclusion

Although no difference between the antagonist protocol and luteal E2 priming protocol groups in terms of IVF outcomes in the DOR patients was found, it seems that the antagonist protocol is the better choice as it allows administration of small doses of gonadotropins, and the duration of ovulation induction is short. Additional prospective and randomized clinical trials are needed to verify the present study's findings.

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