

Comparison of Luteal Phase Estradiol Priming Stimulation Protocol and the Standard Antagonist Protocol in Patients With Diminished Ovarian Reserve Undergoing ICSI

Sezin Erturk Aksakal (✉ drsezert@gmail.com)

Etlik Zubeyde Hanim Women's Health Training and Research Hospital: Zekai Tahir Burak Kadin Sagligi EAH <https://orcid.org/0000-0002-4418-7319>

Oya Aldemir

Etlik Zubeyde Hanim Women's Health Training and Research Hospital: Zekai Tahir Burak Kadin Sagligi EAH

İnci Kahyaoglu

Etlik Zubeyde Hanim Women's Health Training and Research Hospital: Zekai Tahir Burak Kadin Sagligi EAH

İskender Kaplanoğlu

University of Health Sciences Etlik Zubeyde Hanim Women's Health Training and Research Hospital

Serdar Dilbaz

Etlik Zubeyde Hanim Women's Health Training and Research Hospital: Zekai Tahir Burak Kadin Sagligi EAH

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Abstract

Objective

This study aimed to compare the IVF outcomes in patients with diminished ovarian reserve stimulated with luteal phase estradiol (E2) priming protocol versus the standard antagonist protocol.

Methods

The study included 603 patients undergoing intracytoplasmic sperm injection cycles (ICSI) with the diagnosis of diminished ovarian reserve (DOR) who were stimulated with the luteal E2 priming protocol (n=181) and the standard antagonist protocol (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 protocol group than the antagonist protocol group. The number of embryos transferred was higher in the antagonist protocol group compared with the luteal E2 priming protocol group (0.87 ± 0.75 vs. 0.64 ± 0.49 ; $p=0.001$), but there was no statistically significant difference in terms of embryo quality ($p>0.05$). The cycle cancellation rate and the clinical pregnancy and live birth rates per embryo transfer were similar in both groups.

Conclusions

There was no significant difference between the ICSI outcomes of the patients diagnosed with diminished ovarian reserve stimulated with the antagonist protocol and the luteal E2 priming protocol. The antagonist protocol might be considered more advantageous because of the shorter treatment duration and lower doses of gonadotropin, and it allows more embryos to be transferred. Additional randomized controlled trials are needed to verify these findings.

Introduction

Diminished ovarian reserve (DOR) refers to the patients with decreased number and quality of oocytes, and the number of patients attending for in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) treatment cycles with the diagnosis of DOR has increased markedly in the recent years. There is no standard definition for DOR, and the incidence among IVF patients is reported as 10% [1, 2]. The decreased antral follicle count, decreased number of oocytes retrieved, higher cycle cancellation rates, and lower fertilization, implantation, clinical pregnancy, and live birth rates remain to be the significant problems in DOR patients.

Controlled ovarian hyperstimulation (COS) is essential for multifollicular development and is the main step of IVF. The optimal number of oocytes retrieved is important for the 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]. Strategies are recommended for IVF patients with DOR to increase the outcomes, including increasing the gonadotropin dose administered during controlled ovarian stimulation [5], using multiple types of gonadotropins, estradiol priming [6], antagonist protocol, and such alternative supplementation of DHEA, growth hormone [7] and oral L-arginine [8]. Nonetheless, there is no consensus on the optimal stimulation method for increasing IVF treatment's success rate in DOR patients [9].

The present study aimed to compare the IVF outcomes (the number of retrieved oocytes, the cycle cancellation rate, and the clinical pregnancy rate, 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 undergoing ICSI treatment cycles stimulated with a standard antagonist and luteal E2 priming antagonist protocols between January 2007 and July 2019. The study protocol was approved by the Etlik Zubeyde Hanim Women's Health Training and Research Hospital Local Ethics Committee (2019/209). Patients with at least two of the following were diagnosed as DOR: 1) basal serum follicle-stimulating hormone (FSH) level ≥ 12 IU/L and estradiol (E2) level >80 pg/ml measured within the last three months of the IVF cycle, 2) AFC <7 , 3) serum antimullerian hormone (AMH) level <1.1 ng/ml measured in 6 months. Severe male factor infertility, indication for pre-implantation genetic diagnosis (PGD), freeze and thawed embryo cycles, presence of chromosomal or autoimmune disorders, endocrine or metabolic disorders (such as diabetes, hypo/hyperthyroidism, and hyperprolactinemia) were the 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, serum basal FSH, E2, 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 day, the number of retrieved oocytes, mature oocytes, an fertilized oocytes. The number of embryos (good or poor quality) transferred and the E2, P levels, and endometrial thickness on the transfer day were also analyzed. The number of embryo transferred cycles, the number of canceled cycles, day of embryo transfer (day 3 or day 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 gonadotropins with the starting dose of 225-450 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 \geq two follicles reached 13-14 mm during stimulation, the antagonist was initiated (Cetrotide, Merk-Serono, Istanbul, Turkey) and was continued until the recombinant human chorionic gonadotrophin (rechCG) administration day.

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 the menstruation similar with the standart antagonist protocol and when \geq two follicles reached 13-14 mm in diameter, the antagonist, Cetrotide, was initiated and continued until the rechCG administration day.

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 the fertilization. The absence of fertilization was defined as total fertilization failure (TFF). The embryo development was assessed daily, and a development arrest for 24 hours or the presence of an embryo with all cells degenerated or lysed were accepted as embryo development arrest (EDA).

No follicular development with ovarian hyperstimulation, no oocytes retrieved in OPU, and presence of TFF and EDA were considered as cycle cancellation.

The embryo transfer was performed on day 3 or 5 with 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 β -hCG levels in blood tests performed 14 days after OPU. Clinical pregnancy was defined by the presence of an intrauterine gestational sac with fetal cardiac activity by transvaginal ultrasonography. Spontaneous abortion is defined as the loss of a nonviable pregnancy up to 20 weeks of pregnancy. 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 ve histogram. Continuous variables were defined with mean \pm standard deviation, and categorical variables were defined with frequencies and numbers (%). Mann-Whitney U test was used to evaluate comparison between non-normally distributed continuous variables and two-level variables. The Chi-square 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 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; the total antral follicle count did not differ significantly between the two protocol groups ($p > 0.05$) (Table 1). Patients' BMI stimulated with antagonist protocol was significantly higher than the BMI of patients stimulated with luteal E2 antagonist protocol ($p = 0.002$). The serum AMH levels were higher in the antagonist protocol group than the luteal E2 antagonist protocol group (0.53 ± 0.22 vs. 0.26 ± 0.06) ($p = 0.001$) (Table 1).

Table 1

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

	Patients stimulated with antagonist protocol n = 422	Patients stimulated with luteal E2 antagonist protocol n = 181	p
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

FSH: follicle-stimulating hormone; LH: luteinizing hormone; E2: Estradiol P: Progesterone; AMH antimullerian hormone; COS: Controlled ovarian stimulation; hCG human chorionic gonadotrophin. Data presented as mean ± SD. *p* values with statistical significance (*p* ≤ 0.05) are shown in bold

	Patients stimulated with antagonist protocol n = 422	Patients stimulated with luteal E2 antagonist protocol n = 181	p
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. Data presented as mean ± SD. <i>p</i> values with statistical significance (<i>p</i> ≤ 0.05) are shown in bold			

Duration of ovulation induction was significantly longer in the luteal E2 antagonist protocol group than the antagonist protocol group (9.7 ± 2.2 day vs. 9.2 ± 2.0 day; *p* = 0.001). The total gonadotropin dose was also significantly higher in the luteal E2 priming protocol group (3141.76 ± 948.06 IU vs. 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 (*p* > 0.05). The number of embryos transferred was higher in the antagonist protocol group than the luteal E2 antagonist protocol group (0.87 ± 0.75 vs. 0.64 ± 0.49), but the number of good or poor quality embryos transferred did not differ between the groups (*p* > 0.05). Serum E2 level on transfer day was lower, serum P level and the endometrial thickness on transfer day was higher in the luteal E2 antagonist protocol group compared with the antagonist protocol group (*p* > 0.05).

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

Table 2

IVF outcomes of patients stimulated with antagonist protocol and luteal E2 antagonist protocol

	Patients stimulated with antagonist protocol n = 422	Patients stimulated with luteal E2 antagonist protocol n = 181	p
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 follicular 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 Data presented as n(%). <i>p</i> values with statistical significance ($p \leq 0.05$) are shown in bold			

Discussion

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

The definition of DOR varies across studies [10–12]. Baseline FSH, AMH, and AFC are recently used to predict the ovarian reserve [13]. The present study used all four parameters to define diminished ovarian reserve (baseline FSH, baseline E2, AMH, and baseline AFC).

Many different methods are used to treat DOR, but none are superior [9]. The use of the combination of E2 priming and antagonist protocols was first described by Dragisic et al. [14]. Studies have shown that E2 administration during the luteal phase of the previous cycle suppresses the early elevation of FSH and results in homogenous growth in early antral follicles preventing follicular asynchrony [15, 16]. Additionally, a lower cycle cancellation rate, a higher number of ET, and a higher pregnancy rate were noted in patients treated with the luteal E2 priming protocol [17, 18]. Oral estradiol valerate, transdermal estradiol hemihydrate patches, and estradiol pump were used for E2 priming and when compared, it was stated that pregnancy rates were not different between three groups [19].

Most of the studies comparing the luteal E2 priming protocol with the standard antagonist protocol have been published in POR patients [20–22]. 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]. Another study reported no difference in the total gonadotropin dose between the E2 priming protocol and antagonist protocol groups [20]. In the present study, the total gonadotropin dose was significantly higher in the E2 priming protocol group.

Mutlu et al. compared the luteal E2 priming protocol and the standard antagonist protocol, 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 [21]. A retrospective study that included 86 patients 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 [20]. More recently, Lee et al. 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 [22]. The number of retrieved oocyte and mature oocyte and fertilized oocytes did not differ between groups in the present study.

Chang et al. [20] 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 the clinical pregnancy rate and the live birth rate 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 there were not any significant difference between the cycle cancellation rate between the two protocols, similar to the present study. Recently luteal E2 priming protocol with the small number of patients with 4 mg oral E2 was prospectively compared with standard antagonist group and there was no difference in IVF outcomes [23]. One retrospective observational study was published in the literature that compared luteal E2 priming using E2 hemihydrate

and antagonist protocol groups in normoresponders and poor responders. In normoresponders, there was no difference between the groups in terms of IVF outcomes. However, in the poor responder group, pregnancy rate and live birth rate 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, or small patient populations.

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

Conclusions

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

Declarations

Conflict of interest: The authors declare that they have no conflict of interest

Availability of data and material:

Author contributions: All authors contributed to the study conception and design. Aksakal SE: writing of manuscript, literature review, Aldemir O: data collection, data analysis, interpretation of results, Kahyaoglu I: protocol development, review of manuscript, Kaplanoglu I: data collection, Dilbaz S: review of manuscript. All authors read and approved the final manuscript.

Ethics approval: Ethical approval was waived by the local Ethics Committee of University of Health Sciences Etlik Zubeyde Hanim Women's Health Training and Research Hospital in view of the retrospective nature of the study and all procedures being performed were part of the routine care (2019/209).

Declarations of interest: none.

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