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Effect of estradiol pretreatment on antagonist ICSI cycles outcome: A Randomized controlled trial

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Abstract

Background: It was thought that using oral contraceptives or GnRH agonists as a pre-treatment for synchronization of multi-follicular growth and enhancement of COH outcomes offers a higher physiological possibility.

Objective: Investigate whether pretreatment with E2 during the luteal stage influences the growing follicles' development.

Materials and Methods: A randomized controlled trial was performed. 114 infertile couples undergoing intracytoplasmic sperm injection—embryo transfer were included and divided equally into two groups. Group 1: 57 women received estradiol (E2) pretreatment and then underwent an ICSI cycle, Group 2: 57 women who directly underwent ICSI without pretreatment. The ovarian response was evaluated, and A fixed antagonist protocol was employed in both groups. Day 3 ET of good quality embryos were applied.

Results: Group 2 was significantly higher on stimulation days, daily dose of hMG, and gonadotropin ampoules than in Group 1. Number of follicles on day of hCG in group 1 was 9.81± 5.42 and in group 2 was 10.60± 6.54 (P=0.803), also no difference was observed in the number of mature oocytes or the number of high-quality embryos between the two groups. The clinical pregnancy rate was insignificantly increased, in patients received E2, 66.7% vs. 54.4%, in group 1 and group 2, respectively (P = 0.180). The implantation rate increased significantly in group 1 than in group 2 (49.70±41.99% vs. 35.93±39.85%, respectively; P = 0.045).

Conclusions: Estradiol pretreatment in antagonist cycles improves the positive pregnancy rate and implantation rate with a tendency to require lower hMG doses and a shorter stimulation duration.

Keywords: Follicular synchronization; Estradiol pretreatment; antagonist protocol; ICSI

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Introduction

Folliculogenesis is a dynamic process during which a number of follicles undergo the phenomenon of growth. After puberty, each month about 15–20 oocytes would get selected to mature, out of which eventually only one oocyte would ovulate (1). Ovarian stimulation has been used for the purpose of increasing the retrieved oocytes for the purpose of compensating the inefficacy of the IVF technique and empowering the choice of single or extra embryos for transfer. With the GnRH-antagonist (GnRH-ant) protocol, there are concerns about the start times and the potential to gain a useful oocyte number, despite the fact that this can be improved with the use of oral contraceptive pills (OCPs) as a kind of pretreatment method (2). Administration of GnRH-ant is started in the late follicular phase in either a fixed or flexible protocol, with single or multiple doses, with no difference in pregnancy outcome when injection of GnRH-ant (cetrorelix acetate) at 3 mg was compared with each day's dose of ganirelix 0.25 mg (3).
The inability to program the beginning of gonadotrophin induction in GnRH-ant cycles and to minimize weekend pick-up of oocytes is a serious obstacle to the widespread application of the GnRH antagonist protocol in infertility clinics. Scheduling ovarian induction and oocyte pick-up in IVF is essential for the patient, who needs to have fertiltiy treatment at her own convenience, and for the center, which needs to arrange the work tasks (4). Consequently, numerous tries had been derived to deliver the time table of oocyte pick up in a GnRH-ant protocol.
As part of the complex physiological patterns of the human cycle, it has been discovered that in the early days of the follicular stage of the cycle, initial antral follicles vary in size, ranging from 2 to 8 mm in diameter. This will partly be explained by the inconsistent sensitivity to follicle stimulation hormone (FSH) by the developing oocytes during follicular development. This event includes the exposure of initial antral follicles to inclined FSH levels through the late secretory stage (5).
The asynchronous multifollicular growth that appears to be greater in antagonist cycles compared to long-agonist protocols can be an instantaneous outcome of the length heterogeneity of initial antral follicles throughout the initial follicular stages of controlled ovarian induction (6).
There are several ways in which cycle scheduling and follicular synchronization in antagonist cycles can be done, including: -GnRH antagonist pre-treatment (7); pre-treatment with oral contraceptive pills (OCPs) (8, 9); and -estradiol (E2) late luteal phase pre-treatment. The use of oral E2 commenced with the mid-luteal segment of the cycle following previous ovarian stimulation and seems to be an awesome opportunity for cycle scheduling. By inhibiting the increase in FSH that takes place during the luteal follicular transition, it has been shown that luteal E2 pre-treatment inhibits follicular growth. When E2 intake is stopped, the impact ends immediately (10). Similar results to those of the long agonist have been seen when scheduling antagonist cycles with E2 alone, starting in the luteal phase and continuing past the menstrual cycle until the 1st day of stimulation (11).

The aim of this trial was to study the effect of E2 pretreatment in the luteal phase on follicular synchronization during controlled ovarian hyperstimulation (COH) and outcome of antagonist ICSI cycles.

Materials and Methods

Study Design And Participants

This was a prospective randomized controlled trial (RCT) was performed in a private IVF center from June 2020 to February 2021. The Ethics Committee of the Faculty of Medicine at Alexandria University approved the study protocol on June 23, 2020. One hundred and fourteen infertile couples undergoing intracytoplasmic sperm injection—embryo transfer (ICSI—ET) were included. The study was explained to all participants, and written informed consent was obtained. The following inclusion criteria were used for participants selection: women between the ages of 20 and 37 who are undergoing their first or second ICSI cycle have an AMH level > 1.2 ng/ml, and a body mass index (BMI) between 18 and 29 kg/m2. Men with azoospermia or women who had fibroids, endometriosis, uterine

abnormalities, or antral follicular counts (AFC) of fewer than 10 were excluded.

Randomization

The women were randomly divided equally into two groups using a randomization software program: Group 1: 57 women received estradiol (E2) pretreatment and then underwent an ICSI cycle, and Group 2: 57 women who directly underwent ICSI without pretreatment. All participants were subjected to the following: thorough history taking, general and gynecological examination, BMI measurement, and assessment of the infertility workup, including computer-assisted semen analysis (CASA), according to WHO criteria; basal trans-vaginal ultrasound (TVS) to assess AFC and absence of any uterine or pelvic pathology; and a hormonal profile for TSH, prolactin, and AMH levels.

Ovarian stimulation protocol

Group 1: women received 4 mg estradiol valerate (Progynova 2 mg; Bayer) once daily beginning one week after ovulation in the preceding cycle or 5 days before the anticipated start of menstruation. With the onset of menstruation, E2-pretreatment was stopped, and COH was begun one day later with a dosage of hMG ranging from 225 to 375 IU, depending upon the clinical evaluation using patient ovarian reserve, BMI, woman's age, and previous response to ovulation induction if available. **Group 2:** women received stimulation at a dose of 225–375 IU of hMG according to the same clinical evaluation starting on cycle day 2 without E2 pretreatment. The ovarian response and endometrial status were evaluated by vaginal ultrasound on the 5th day of stimulation, then every other day to adjust the dose of stimulation. A fixed antagonist protocol was employed in both groups, with the administration of cetrorelix (cetrotide 0.25 mg, Merck) daily starting from the 5th day of stimulation until the day of hCG administration. When three or more follicles have at least a mean diameter of 18 mm or more, triggering of oocyte maturation was performed using 10.000 IU of human chorionic gonadotropin (hCG) (Choriomon® 5000 IU, IBSA Switzerland), and oocyte retrieval was performed after 36 hours.

Assisted reproduction technique

Oocyte pick-up is performed under general anesthesia by transvaginal approach under ultrasound guidance. Participants received luteal phase support after oocyte retrieval in the form of vaginal progesterone suppositories at a dose of 600 mg/day (Prontogest Supp®, Marcyrl). After oocyte denudation and sperm preparation, ICSI was performed on all mature metaphase II (MII) oocytes. Oocytes were examined for fertilization 16–18 hours after ICSI. Day 3 embryos were scored according to number, symmetry of blastomeres, and degree of fragmentation. On day 3 of ICSI, under transabdominal ultrasound guidance, embryos of the best quality were transferred using an ET catheter (Labotect), connected with a 1 ml syringe through the cervix, and the embryos were gently deposited 1.5 cm from the fundus. The catheter was withdrawn carefully and slowly. 14 days after the ET, a pregnancy test was done.

Outcome measures

The primary outcome measures were: days of stimulation, the total number of gonadotropin ampoules used and on the day of hCG: the total number of follicles by U/S, serum E2, progesterone levels endometrial thickness and the number of MII oocytes, and good-quality embryos. The secondary outcome measures were: pregnancy rate, diagnosed by serum B-hCG assay 14 days after ET; clinical pregnancy rate, determined when fetal heart beat observed 2 weeks after a positive pregnancy test by transvaginal ultrasonography (TVS).

Statistical analysis

Using IBM SPSS software, version 20.0, the data that were entered into the computer were analyzed (IBM Corp., Armonk, NY). A percentage and a number were used to represent quantitative information. The range (minimum and maximum), mean, standard deviation, and median were the descriptive statistics for quantitative data. The results' statistical significance was determined at the

5% level. The Student t-test, Chi-square, Mann Whitney, and Monte Carlo tests were used.

Results

This study included a total of 114 women who were randomized into two groups: 57 infertile women received estradiol pretreatment before ICSI (Group 1), and 57 underwent ICSI without any pretreatment (Group 2). The outcomes of 114 participants were analyzed. The baseline data was comparable between the two groups, including female age, BMI, type of infertility (primary or secondary), first or second ICSI trial, and AMH level. Primary infertility represented 73.7% of cases in group 1 and 64.9% in group 2, while secondary infertility represented 26.3 % and 35.1%, respectively (P = 0.210). First ICSI cycles represented 54.4% in group 1 and 56.1% in group 2, while second ICSI cycles represented 45.6 % and 43.9 % in group 1 and 2, respectively, with P= 0.851. The mean AMH level was 2.23 ng/ml ± 1.59 in group 1 versus 2.81 ng/ml ± 2.52 in group 2, P = 0.302 (Table 1).

Table 1: Baseline characteristics of the studied groups.

	Group 1 (N=57)	Group 2 (n-57)	Test of significance	p
Female age (years)				
Min. – Max.	23.0 – 37.0	22.0- 37.0		
Mean ± SD.	31.49±4.15	32.16±4.17	t=0.856	0.394
Median (IQR)	31.0(28.0-35.0)	33.0(28.0-36.0)		
BMI (kg/m2)				
Min. – Max.	21.48-28.79	21.20-28.96		
Mean ± SD.	26.75±1.75	26.78±2.13	t=0.080	0.937
Median (IQR)	27.39 (25.6-27.9)	27.64 (25.4-28.4)		
Type of infertility				
Primary % (no.)	73.7 (42)	64.9 (37)	$\chi 2$ =1.031	0.210
Secondary % (no.)	26.3(15)	35.1(20)		
ICSI cycle				
1st	54.4 (31)	56.1(32)	$\chi 2$= 0.035	0.851
2nd	45.6 (26)	43.9 (25)		
AMH (ng/mL)				
Min. – Max.	1.23 - 9.70	1.24- 11.20		
Mean ± SD.	2.23 ± 1.59	2.81 ± 2.52	U= 1442.5	0.302
Median (IQR)	1.49 (1.4-2.2)	1.63 (1.4-2.6)		

t: **Student t-test** χ^2: Chi-**square test** U: **Mann Whitney test.**
SD**: Standard deviation** IQR: **Inter quartile range** no.**: number**
p: p value for comparing between the two groups.
Group 1: Estradiol pretreatment **Group 2:** No Estradiol pretreatment

When the ICSI cycle outcomes of the two groups were compared, there was a significant improvement in some of the cycle characteristics with E2 pretreatment, as shown in table 2.

Table 2: Cycle characteristics of the two studied groups.

	Group 1 (n=57)	Group 2 (n=57)	Test of significance	p
Stimulation (days)				
Min. – Max.	7.0-15.0	7.0-15.0		
Mean ± SD.	10.49±1.86	11.40±1.84	U=1360.5	0.049*
Median (IQR)	10.0(9.0-12.0)	11.0(10.0-13.0)		
Daily dose of hMG				
Min. – Max.	225.0-375.0	225.0-375.0		
Mean ± SD.	320.18±63.81	342.89±52.12	U=1314.5*	0.048*
Median (IQR)	375(225.0-375.0)	375(300.0-375.0)		
Total number of gonadotropin ampoules 75 IU				
Min. – Max.	24.0-75.0	27.0-75.0		
Mean ± SD.	44.68±11.41	52.25±11.65	U=1221.5*	0.041*
Median (IQR)	45.0(35.0-50.0)	55.0(44.0-60.0)		
Serum estradiol on day of hCG				
Min. – Max.	584.0- 7327.0	698.0- 6330.0		
Mean ± SD.	2007.6± 1398.3	2609.5± 1618.0	U=1285.5	0.055
Median (IQR)	1641(1054- 2421)	2215(1138- 3896)		
Serum progesterone on day of hCG				
Min. – Max.	0.09 – 1.55	0.07 – 1.60		
Mean ± SD.	0.67±.37	0.69±0.39	U=1559.0	0.710
Median (IQR)	0.63(0.45-0.85)	0.66(0.38-0.87)		
Endometrial thickness on day of hCG (mm)				
Min. – Max.	8.0 – 14.0	8.0 – 15.0		
Mean ± SD.	10.45± 1.52	10.37± 1.55	t=0.280	0.780
Median (IQR)	10.0(9.50-11.50)	10.0(9.0-11.0)		
Number of follicles on day of hCG				
Min. – Max.	3.0 – 24.0	3.0 – 25.0		
Mean ± SD.	9.81± 5.42	10.60± 6.54	U=1580.5	0.803
Median (IQR)	8.0(6.0-12.0)	8.0(5.0-14.0)		
Number of mature oocytes				
Min. – Max.	1.0 – 23.0	1.0 – 20.0		
Mean ± SD.	6.81± 5.08	7.07 ± 4.96	U=1557.5	0.703
Median (IQR)	6.0(3.0-9.0)	5.0(4.0-10.0)		
Ratio of no. mature oocytes to no.follicles on day of hCG				
Min. – Max.	0.17 – 1.0	0.16 – 1.0		
Mean ± SD.	0.69 ± 0.29	0.69 ± 0.25	U=1588.0	0.835
Median (IQR)	0.75(0.43-1.0)	0.75(0.50-0.92)		
Number of good quality embryos				
Min. – Max.	1.0 – 13.0	1.0 – 20.0		
Mean ± SD.	4.25± 2.73	4.81 ± 3.66	U=1515.5	0.532
Median (IQR)	4.0(2.0-6.0)	4.0(3.0-6.0)		
Number of embryos transferred				
Min. – Max.	1.0 – 3.0	1.0 – 3.0		
Mean ± SD.	2.23± 0.68	2.30 ± 0.78	U=1507.0	0.470
Median (IQR)	2.0(2.0-3.0)	2.0(2.0-3.0)		

U: **Mann Whitney test.** t: **Student t-test**
SD**: Standard deviation** IQR: **Inter quartile range**
*: Statistically significant at $p \leq 0.05$
Group 1: Estradiol pretreatment Group 2: No Estradiol pretreatment
p: p value for comparing between the two groups.

In group 1, the mean of stimulation days was 10.49±1.86 days significantly lower than the mean of stimulation days in group 2: 11.40±1.84 (P = 0.049), and the daily dose of hMG was significantly higher in group 2, with a mean of 320.18±63.81 and 342.89±52.12 in groups 1 and 2, respectively (P = 0.048). Group 2 had significantly more gonadotropin ampoules, with a mean of 52.25±11.65 ampoules, whereas a mean of 44.68±11.41 ampoules in group 1 (P = 0.041) (Table 2). However, the mean serum E2 level on the day of hCG was comparable: 2007.6±1398.3 pg/dl in group 1 and 2609.5± 1618.0 pg/dl in group 2, p = 0.055. Similarly, progesterone levels on hCG day ranged from 0.09 to 1.55 ng/dl with a mean value of 0.67±0.37 ng/dl in group 1, and from 0.07 to 1.60 ng/dl with a mean value of 0.69±0.39 ng/dl in group, P = 0.710 (Table 2).

On day of hCG in group 1, the endometrial thickness ranged from 8.0 to 14.0 mm (mean 10.45±1.52 mm), while in group 2, it ranged from 8.0 to 15.0 mm (mean 10.37±1.55 mm), p = 0.780 (Table 2). The mean number of follicles on day of hCG in group 1 was 9.81± 5.42 and in group 2 was 10.60± 6.54 (P=0.803), also no difference in the number of mature oocytes between the two groups with a mean value of 6.81±5.08 oocytes and 7.07±4.96 oocytes for group 1 and 2 respectively, P =0.703. The ratio between the number of mature oocytes to the number of follicles on day of hCG in group 1 ranged from 0.17 – 1.0 with a mean of 0.69 ± 0.29 and in group 2 ranged from 0.16 – 1.0 with a mean value of 0.69 ± 0.25 (P =0.835). Additionally, there was no significant difference in the quantity of high-quality embryos between the two groups nor in the number of embryos transferred. Good quality embryos ranged from 1.0 –13.0 embryos with a mean value of 4.25±2.73 in group 1 and ranged from 1.0 to 20.0 embryos with a mean value of 4.81±3.66. in group 2, p = 0.532. In group 1, one to three embryos were transferred with a mean value of 2.23±0.68, and in group 2, one to three embryos were transferred with a mean value of 2.30±0.78, P = 0.470 (Table 2).

Regarding the clinical outcomes (Table 3), the pregnancy rate was significantly higher in group 1 than in group 2 (77.2% versus 59.6%, respectively); p = 0.044, with no statistically significant difference in the clinical pregnancy rate or in the number of gestational sacs. The clinical pregnancy rate was increased, 66.7% vs. 54.4%, in patients who received E2 pretreatment (group 1) and patients without E2 pretreatment (group 2), respectively (P = 0.180). In group 1, there were one gestational sac (GS) in 25 (56.8 %) women, two GS in 13 (29.5%) women, and three GS in 6 (13.6%) women, while in group 2, 24 (70.6%) women had one GS, 9 (26.5%) women had two GS, and one woman (2.9%) had three GS, MCP = 0.231. The implantation rate, the ratio between gestational sacs number and the transferred embryos number, increased significantly in group 1 than group 2 (49.70±41.99% vs. 35.93±39.85%, respectively; P = 0.045) (Table 3).

Discussion

Higher patient acceptance is a characteristic of GnRH-antagonist cycles, and in order to plan antagonist cycles, greater focus is placed on the initial effects of steroidal pretreatment, as noticed size discrepancies of developing oocytes reflect unarranged development of the follicular-oocyte combination and complicate medical standards for hCG administration. Less MII oocytes and developing embryos are linked to this phenomenon, which limit embryo choice for ET. In fact, the number of available good quality embryos is an essential prognostic factor for outcomes, particularly in patients with bad prognosis; it is likely that by increasing the likelihood, at least one good to excellent embryo will be chosen for ET. Techniques for ovarian stimulation have been developed as a result of a greater understanding of follicular growth during COH (12, 13). It was thought that using oral contraceptives or GnRH agonists as a pre-treatment for synchronization of multi-follicular growth and enhancement of COH outcomes offers a higher physiological possibility.

The current study is a RCT that looked into whether pretreatment with E2 during the luteal stage influences the growing follicles developmental criterion within COH. It relied on the speculation that increased antral follicle synchronization is an effect of the sluggish FSH increase that happens for the duration of the overdue luteal phase, thus testing to determine

how luteal E2 affects follicular synchronization and the outcome of ICSI.

We recruited fifty-seven cases in the E2 pretreatment group and fifty-seven cases in the

Table 3: **Clinical outcomes of the two studied groups.**

	Group 1 (n=57)	Group 2 (n=57)	Test of significance	p
Pregnancy test % (no.)				
Negative	22.8 (13)	40.4 (23)	$\chi 2$=4.060*	0.044*
Positive	77.2 (44)	59.6 (34)		
Clinical pregnancy % (no.)				
Yes	66.7 (38)	54.4 (31)	$\chi 2$=1.799	0.180
No	33.3 (19)	45.6 (26)		
No. of sacs % (no.)	(n = 44)	(n = 34)		
1	56.8 (25)	70.6 (24)	$\chi 2$=2.924	MCp=0.231
2	29.5 (13)	26.5 (9)		
3	13.6 (6)	2.9 (1)		
Implantation rate				
Min. – Max.	0.0 – 200.0	0.0 – 200.0		
Mean ± SD.	49.70±41.99 %	35.93±39.85 %	U=1281.5*	0.045*
Median (IQR)	50.0(0.0-67.0)	33.0(0.0-50.0)		

χ^2: **Chi square test**
SD**: Standard deviation**
Group 1: Estradiol pretreatment
p: p value for comparing between the two groups.
U: **Mann Whitney test.**
IQR: **Inter quartile range no.: number**
Group 2: No Estradiol pretreatment
*: Statistically significant at $p \leq 0.05$

group without pretreatment.

Our results detected that the daily dose of hMG was significantly higher within group 2 (without pretreatment) than the E2 pretreatment group (P = 0.048); also, the days of stimulation and number of gonadotropin ampoules used were significantly higher in group 2 with (p = 0.049, 0.041, respectively). Pregnancy tests were positive in 77.2 % of cases in the pretreatment group and 59.6 % of cases in the other group which is significantly higher in E2 pretreatment cases (p = 0.044). The percentage of implantation was significantly higher in the E2 pretreatment group (P = 0.041). However, no significant statistical difference was found between the two studied groups with regard to the female age, BMI, infertility type, number of ICSI cycles, AMH level, serum E2 and progesterone, endometrial thickness, follicles number on day of hCG, developed oocytes number, good quality embryos, pregnancy sacs number, clinical pregnancy rate, the ratio of developed oocytes to the number of follicles on triggering day and number of embryos transferred.

As our study demonstrated, the days of stimulation with gonadotropin, the total number of gonadotropin ampoules used, and all the daily administered hMG were significantly higher in patients without pretreatment. Lee et al investigated whether or not luteal estrogen (E) treatment and an early follicular GnRH- ant (E/G-ant) priming enhance cycle outcomes for IVF-ET (14). This retrospective study analyzed outcome of 65 poor responders who received the E/G-ant priming protocol and 64 poor responders who underwent the traditional protocol with no pretreatment. In agreement

with our results, they found a longer duration of stimulation in the control group (10.00±1.95 days vs. 9.85±1.95 days) but did not reach significance (P = 0.995).

Ce´drin-Durnerin et al in a RCT, studied the consequences of E2 pretreatment in GnRH-ant cycles. 238 patients were allocated to the E2 pretreatment group, and 234 patients to the no pretreatment group. Total FSH supply (1557 408 vs. 1389 347 IU) and days of stimulation (10.8 1.4 vs. 10.0 1.5 days) were marginally but significantly increased in the E2 group, whereas no significant statistical difference was found in the total daily dose of FSH (162 31 vs. 158 30), in contrast to our study, despite the similar starting dose in both groups and total FSH supply used in stimulation that was significantly higher than in the E2 pretreatment group. This may be due to the longer duration of stimulation with the serum E2, which was also higher in the pretreatment group. The authors detected that pre-treatment with E2 is correlated with the need for higher FSH doses and prolonged periods of induction without any significant elevation in the oocytes retrieved. They concluded that E2 has no effect on cycle outcome and thus may be used in clinical work to plan IVF retrievals over days of work (15).

In contrast to our study, Chang et al conducted a study to verify whether giving E2 in the luteal stage of the proceeding cycle in GnRH-ant cycles could improve follicular response and hence enhance outcome in poor responders (16). They discovered that the amount of gonadotropin used in the luteal E2 cases was significantly higher than in the standard GnRH-ant protocol cases (2356.3 824.8 vs. 1980.9 714.9 IU) (P = 00.004), which could be attributed to the study being conducted on poor responders.

In our study, there was no significant statistical difference in serum E2 and progesterone levels on triggering day. Fanchin et al conducted a study to investigate if E2 pretreatment decreased discrepancy in the size of follicles and strengthened the ovarian response in the recombinant FSH (r-FSH)/GnRH-ant protocol that included 47 patients within the E2 pretreatment group who took micronized 17b-estradiol tablets (4 mg/day) given orally and 43 patients within the control group without pretreatment (17). They found no statistical significance in serum E2 and progesterone levels on the day of the trigger between the two groups, which is consistent with our findings.

There was no statistical difference observed between the two groups in our results concerning the follicles number detected using ultrasound on hCG day. In agreement with our study, Rashidi et al analyzed the impact of E2 pretreatment with GnRH antagonist on on the synchronization of antral follicular size and baseline hormone levels (18). They observed no large distinction as regards the detected number of follicles on the day of hCG (p=0.648). In contrast, Fanchin et al in their study, found a significantly higher follicles number on the day of hCG (9.9 6±0.5 vs. 7.96 ±0.5 (p <0.01) (17). This could be due to E2 pretreatment in cases that required a higher r-FSH dose than the other group in their study (2674 91 vs. 2463 100 IU), but the difference was not significant (18).

Our findings revealed no significant difference between the studied groups in terms of ET on the day of hCG (p = 0.780).Ensieh Shahrokh et al conducted a RCT in which 210 females underwent IVF with the GnRH-ant protocol that was randomly assigned to the OCP, estradiol, or no pretreatment (19). In accordance with our study, they found no significant statistical distinction as regards the ET on the day of hCG.

In addition, our results detected no significant statistical distinction as concerning the range of good quality embryos and transferred embryos, Blockeel et al in a RCT, compared the influence of E2 pretreatment with E2 valerate all through the luteo-follicular period in antagonist cycles (20). They discovered no statistically significant difference in terms of the range of good embryos (9.9 7.8 vs. 10.0 4.7), which is similar to our findings.

Chang et al detected that the quantity of good-quality embryos and the quantity of transferred embryos have been better in the pretreatment group (p=0.047, p=0.014, respectively), which contradicts our findings (16). This may be related to the gonadotropin dose being increased with the luteal E2, and this can mirror a steadier and more harmonized stimulation method due to the stepped-forward similarity of antral follicles. Also, the pretreatment group in this study included two different luteal E2

protocols: one protocol stopped E2 in the 3rd day of the following cycle, and the other protocol extended E2 intake during stimulation; this would strengthen the inducing influence of FSH on granulosa cell follicle stimulating hormone receptors and ameliorate embryo quality.

Furthermore, Aubead et al investigated the effects of the luteal phase protocol via E2 versus GnRH antagonist on hormonal levels, coordination of antral follicular size, and ICSI outcomes (21). The study included 20 females in every group, either with E2, cetrorelix acetate, or no pretreatment. They noticed a better range of MII in the E2 pretreatment group (7.3 to 6.3). This can also be a result of using a flexible protocol; however, we used a fixed antagonist protocol.

Reynolds et al found that women exposed to luteal E2 priming had an improved pregnancy rate, and there was no significant enhancement in the number of mature oocytes that resulted or the number of embryos produced in a cycle compared with women subjected to non-LE pretreatment protocols (patients = 621). Our results agree with this (22).

A retrospective study of Dragesic et alconducted to detect the effect of use of a luteal E2 patch and prior to gonadotropin induction for IVF in antagonist protocol, they included 68 prior poor responders in 80 IVF cycles (23). Contrary to our study there were increase in count of developed oocytes and count of good quality fertilized ovum obtained, this may result from the increased close of gonadotropin ampoule given in E2 patches group.

In our study, there was comparable MII number and the ratio of mature oocytes to the number of follicles at the time of hCG in both groups (p = 0.835). In concordance, Shahrokh et al found no significant differences in the mature oocyte and embryonic condition (19). They concluded that E2 pretreatment could ameliorate the fresh IVF-ET outcomes. In addition, in accordance with our outcomes, the study conducted by DiLuigi AJ et al showed that E2 priming in a GnRH-ant cycle had no impact on IVF outcomes regarding the resultant follicles and oocytes (24).

Fanchin R et al determined that embryos transferred similar in compared groups, with improved pregnancy rate with the E2 pretreated patients which is in line with our results (17).

The implantation rate was significantly increased in our E2 pretreatment group. Similarly, Chang et al detected a significantly higher implantation rate with E2 pretreatment (p = 0.020) (16).

Contrary to our results, Saple et al conducted a study to detect the benefits of E2 in the luteal phase of the previous cycle (25). They determined that there have been no variations in normal IVF/ICSI outcomes; E2 pretreatment protocol produces exceedingly low implantation and pregnancy rates.

The inconsistent findings between studies may be due to a variety of risk factors, including treatment failure or a poor response to therapy, disparities in sample size, and difference in the severity of the condition in the studied group. As regards our study, the observed significantly increased pregnancy and embryo implantation rates, despite a comparable oocyte number and ratio of developed oocytes to follicles number at the time of hCG in both groups, seem impressive. The current data do not imply an increase in the number of mature oocytes or the count of better quality fertilized oocytes, but embryo implantation and pregnancy rates with luteal E2 pretreatment may indicate a quality improvement in follicular media, warranting further investigation.

Conclusion

In conclusion, estradiol pretreatment in antagonist cycles improves the positive pregnancy rate and implantation rate with a tendency to require lower doses of hMG and a shorter duration of stimulation.

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