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GnRH agonist administration as luteal support on the transfer day of single blastocyst in dual-triggered cycles

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ABSTRACT

Objectives: Luteal phase support with gonadotropin-releasing hormone agonist (GnRH-a) has been considered in terms of its potential beneficial effects on in vitro fertilisation (IVF) cycles. In our study, we assessed the effectiveness of single-dose GnRH-a administration in dual-triggered cycles on pregnancy outcomes.

Material and methods: Eighty women who underwent intra cytoplasmic sperm injection (ICSI) cycle and had fresh blastocyst transfer were divided into two groups in terms of luteal phase support. The study group (Group A) consisted of patients (n = 40) who received a single-dose GnRH-a injection (0.1 mg of triptorelin acetate) subcutaneously 6 days after oocyte retrieval in addition to 600 mg daily of micronised progesterone, and the control group (Group B) comprised of patients (n = 40) taking 600 mg micronised progesterone daily from the first day after oocyte retrieval. GnRH-a and human chorionic gonadotropin (hCG; dual trigger) were administered to all patients. Comparison of the clinical pregnancy and live birth rates was our main goal.

Results: There was no significant difference between the two groups in terms of β-hCG positivity rates, clinical pregnancy rates and live birth rates (p value for beta-hCG = 0.25, clinical pregnancy = 0.80, live birth = 0.45).

Conclusions: Our study demonstrated that in dual triggered cycles administration of a single dose of GnRH-a on the transfer day of a single blastocyst in addition to routine luteal phase support with progesterone does not statistically increase implantation, clinical pregnancy or live birth rates.

Key words: GnRH agonist; luteal phase support; IVF

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INTRODUCTION

In artificial reproductive technology (ART) cycles, luteal phase deficiency is a common problem that may affect in vitro fertilisation (IVF) success. The ideal method of luteal phase supplementation remains controversial; thus, various regimens have been implemented[1]. Basically, synthetic or natural forms of progesterone have been administered via different routes. Furthermore, human chorionic gonadotropin (hCG), which has both a similar molecular structure and physiological effects to luteinising hormone (LH), has been implemented [1]. Finally, many studies illustrating the effectiveness of GnRH-a use have been reported in the literature and data from recently published articles have suggested the beneficial effects of GnRH-a administration in terms of luteal phase support in IVF cycles [1, 2]. However, there is no consensus on the best luteal phase regimen. On the other hand, dual trigger using hCG and GnRH-a together has been demonstrated to have better IVF outcomes in several studies for both normal and poor responder patients.

Objectives

We aimed to evaluate the effects of additional single-dose GnRH-a administration to progesterone use in dual triggered cycles.

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MATERIAL AND METHODS

Patient population

We conducted a retrospective study at the University of Health Sciences, Tepecik Training and Research Hospital IVF Centre between May 2018 and November 2020. The medical records of 396 infertile patients with unexplained infertility and low ovarian reserves were examined.

Eighty patients were enrolled in the study. Among these patients, 40 who had their first IVF trial, single blastocyst transfer and single dose GnRH-a administered after five days of embryo transfer were selected as the study group. Meanwhile, 40 patients with the same indications without GnRH-a administration were selected as the control group. In both the study and control groups, 27 patients had unexplained infertility and 13 patients had low ovarian reserve. Low ovarian reserve is defined as an antral follicle count (AFC) < 5–7 or antimullerian hormone (AMH) level < 0.5–1.1 ng/mL according to the Bologna criteria of ESHRE consensus [3].

Patients with further infertility factors like polycystic ovarian syndrome (PCOS), tubal factor and male factor, as well as patients older than 40 years of age, patients who had a previous IVF trial and patients who had more than one embryo transfer were not included. The study was approved by the Institutional Review Board of the University of Health Sciences, Tepecik Training and Research Hospital, Izmir, Turkey (2021/11-21). Informed consent was obtained from the study participants.

Hormonal and ultrasound assessments

Suitable patients were evaluated on Day 2 or 3 of the menstrual cycle regarding endometrial thickness, antral follicle count and presence of any ovarian cyst with the help of 5 MHz transvaginal ultrasound. Blood samples to measure serum follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), progesterone (P) and thyroid-stimulating hormone (TSH) were taken.

Ovarian stimulation

Recombinant FSH (Gonal-F; Merck-Serono, Istanbul, Turkey) or urofollitropin (Fostimon; IBSA, Istanbul, Turkey) and highly purified hMG (Merional; IBSA) at doses ranging between 150 and 300 IU/day were initiated on Days 2 or 3 of menstrual bleeding. Gonadotropin dosages were regulated according to the ovarian response. The ovarian response was monitored using transvaginal ultrasound and E2 levels. Flexible GnRH antagonist protocol (Cetrotide, 0.25 mg/day, Merck-Serono) was initiated when the leading follicle was 13––14 mm in average diameter and/or the serum E2 concentration was greater than 350 pg/mL and continued until the day of hCG administration. Dual trigger with 250 µg of recombinant hCG (Ovitrelle; Merck-Serono) and 0.25 mg of triptorelin (Gonapeptyl; Ferring, Istanbul, Turkey) were given upon detection of at least two follicles with a mean diameter of 17 mm. All patients underwent blastocyst transfer on Day 5. A single dose of 0.25 mg of triptorelin was administered for luteal phase support.

IVF/ICSI procedures

Oocyte retrieval was performed using transvaginal ultrasonography under general anaesthesia 35.5 hours after the ovulation was triggered, by using a 17-gauge double-channel needle (Cook IVF, Cook, Australia) and fertilised using conventional ICSI and cultured until the transfer day. The embryo quality was assessed in the embryo cleavage stage and the blastocyst stage. A single embryo was transferred on Day 5 using transabdominal ultrasound guidance. The luteal phase was supported with only vaginal progesterone gel in the control group (Crinone; Actavis, USA), starting on the day of oocyte retrieval and continuing until 12 weeks of pregnancy in case pregnancy was detected. In the trial group, a second dose of 0.25 mg of triptorelin was given subcutaneously on the day of embryo transfer in addition to vaginal progesterone.

Outcome measurements

The main outcomes were comparison of chemical and clinical pregnancy and live birth rates. Serum levels of β-hCG were measured to confirm pregnancy on Day 12 after embryo transfer. β-hCG level greater than 5 IU/L was accepted to be positive. Detection of fetal heartbeat at 6 weeks of gestation using vaginal ultrasound was defined as clinical pregnancy. Delivery of a live infant after 24 gestational weeks was defined as live birth. Secondary outcomes were number of collected oocytes, fertilisation rate, endometrial thickness on transfer day and number of embryos reaching Day 5.

Statistical analysis

SPSS for Windows version 23.0 (SPSS, Chicago, USA) was used for statistical calculations. Mean values were expressed as mean ± standard deviation. Student's t-test for continuous variables and chi-square test or Fisher's exact test for categorical variables were used for statistical comparisons. A p value of < 0.05 was considered statistically significant.

RESULTS

Table 1 illustrates the patient characteristics and basal hormone levels. No significant differences were observed as regards duration of menstruation, body mass index, age, total antral follicle count, Day-3 serum FSH, Day-3 serum E2, TSH, PRL and AMH levels. Furthermore, regarding paternal age and total progressive motile sperm count (TPMSC) there were no significant difference.

Table 1. Patient characteristics and basal hormone levels

Parameters	Study group (n = 40)	Control group (n = 40)	p value
Age [years]	30.83 (± 3.80)	32.23 (± 2.77)	0.27
BMI [kg/m^2]	24.60 (± 4.35)	24.34 (± 3.07)	0.67
Menstrual cycle [days]	28.05 (± 3.77)	27.80 (± 1.52)	0.19
Paternal age [years]	33.88 (± 4.02)	34.03 (± 3.21)	0.49
Duration of marriage [years]	6.15 (± 4.02)	5.73 (± 2.81)	0.71
Duration of infertility [years]	4.26 (± 2.91)	4.51 (± 2.33)	0.46
Total antral follicle count	11.43 (± 4.34)	9.38 (± 7.33)	0.31
Day-3 serum FSH [mIU/mL]	9.37 (± 4.39)	8.33 (± 3.41)	0.68
Day-3 serum E2 [pg/mL]	46.34 (± 33.60	40.15 (± 13.01)	0.52
TSH [IU/mL]	4.05 (± 5.03)	2.92 (± 1.09)	0.12
PRL [ng/mL]	15.64 (± 7.82)	20.88 (± 7.89)	0.80
AMH [ng/mL]	1.82 (± 1.20)	1.13 (± 0.23)	0,68
TMSC [Million]	16.20 (± 10.75)	13.23 (± 7.28)	0.36

Values are mean ± SD (range) or percentage (number/total); p values less than 0.05 were considered statistically significant. There were no statistically significant differences between the two groups; BMI — body-mass index; TMSC — total motile sperm count; FSH — follicle-stimulating hormone; LH — luteinizing hormone; E2 — estradiol; P — progesterone; AMH — anti-mullerian hormone; TSH — thyroid-stimulating hormone; PRL — prolactin

Table 2. Comparison of ovarian stimulation outcomes

	Study group	Control group	p value
Duration of stimulation	8.83 ± 1.81	8.65 ± 1.52	0.57
Gonadotropin starting day	2.45 ± 0.52	2.23 ± 0.57	0.053
Total dosage of gonadotropins	2218.44 ± 736.65	2214.38 ± 710.699	0.68
Antagonist starting day	6.95 ± 0.98	6.70 ± 0.99	0.73
Duration of antagonist usage	4.65 ± 1.33	4.83 ± 0.93	0.61
HCG application day	10.95 ± 1.89	10.83 ± 1.46	0.11
ET at HCG day	9.75 ± 1.68	9.39 ± 1.95	0.69
E2 level at HCG day	1543.29 ± 838.85	1472.35 ± 630.56	0.22
Progesteron level at HCG day	1.23 ± 0.71	0.99 ± 0.33	0.054

Values are mean ± SD (range) or percentage (number/total); Study group = using GnRH agonist on 5th day of embryo transfer group; Control group = progesteron only; p values less than 0.05 were considered statistically significant; HCG — human chorionic gonadotropin; E2 — estradiol; ET — endometrium thickness

Table 2 depicts the comparison of ovarian stimulation outcomes and the degree of ovarian stimulation in both groups. The initial dose of gonadotropins, duration of ovarian stimulation, total dosage of gonadotropins, antagonist starting day and duration of antagonist use were comparable. Moreover, endometrial thickness and serum concentrations of E2 on the trigger day showed no significant differences. Finally, the quality of the embryos transferred was similar. However, differences in the progesterone level at hCG day was observable, although it was not statistically significant.

Table 3 demonstrates the pregnancy outcomes. There were no significant differences in terms of beta-hCG positivity rate, clinical pregnancy rate and live birth rate (p = 0.25, 0.80 and 0.45, respectively).

Table 3. Pregnancy outcomes

	Chemical pregnancy rate [%]	Clinical pregnancy rate [%]	Live birth rate [%]
Study group	70.0 (28/40)	52.5 (21/40)	37.5 (15/40)
Control group	67.5 (27/40)	65 (26/40)	40.0 (16/40)
Total	68.7 (55/80)	58.7 (47/80)	38.7 (31/80)

There were no statistically significant differences between two groups. p value for beta- hCG positive: 0.25, clinic pregnancy: 0.80, live birth rate: 0.45

DISCUSSION

To the best of our knowledge and according to PubMed search, no study has ever examined the effects of GnRH-a addition as luteal phase support on the transfer day of single

blastocysts in dual-triggered cycles. The GnRH-a has been used in ovarian stimulation in ART cycles, particularly in patients who have been classified as hyper-responders; moreover, recently it has been used for luteal phase support both in fresh and frozen-thawed embryo transfer cycles [4]. The underlying mechanism of GnRH-a in luteal phase support remains unclear. Stimulating LH secretion from hypophysis and activating GnRH receptors on endometrium have been suggested as possible mechanisms for corpus luteum support. This may have important roles in process of implantation. Moreover, there may be a direct effect of GnRH-a on early embryos. Finally, GnRH-a may have effect on in vivo and in vitro placental hCG production [5].

In the early 2000s, Pirard et al. [5] conducted a study comparing the effectiveness of GnRH-a administration versus hCG with micronised progesterone on luteal phase support and reported that GnRH agonist (buserelin) alone may be effective in triggering follicle maturation and luteal phase support. Later in 2015, the author published another study revealing the effectiveness of continuous, low-dose GnRH agonist administration as luteal phase support and concluded that the efficacy of the stated protocol was comparable to the use of hCG with micronised progesterone in terms of pregnancy rate, implantation rate and clinical pregnancy rate [6]. However, although there was no significant difference, these parameters were observed to be higher in the hCG-micronised progesterone group. In addition, progesterone levels were reported to be lower in the GnRH-a group [6]. In another study, Jan Tesarik et al. published an article illustrating the positive effect of GnRH-a administration in patients who had low serum progesterone levels in the luteal phase of their first IVF cycle and reported that there was an increase in ICSI outcomes depending on the luteal phase support with GnRH agonist [7]. Tesarik et al. [8] investigated the use of GnRH agonist on patients with luteal phase deficiency and found that administration of GnRH agonist after embryo transfer improved the chance of pregnancy and birth rate. In 2009, Isık et al. [9] published an article that demonstrated the effect of single-dose GnRH-a (0.5 mg leuprolide acetate) administration 6 day after ICSI procedure together with micronised progesterone as a luteal phase support and reported that the implantation and clinical pregnancy rates were statistically higher. A meta-analysis conducted by Kyrou et al. [10] demonstrated a positive effect for GnRH-a on improving clinical pregnancy and live birth rates.

On the other hand, numerous studies have reported no benefit of GnRH-a therapy in terms of luteal phase support. In 2012, Inamdar et al. [11] analysed the effects of GnRH-a administered 6 days after oocyte retrieval as an adjunct to progesterone and reported no superiority to routine luteal phase support with progesterone. In this study, implantation and clinical pregnancy rates were found to be similar to those of the control group. In another randomised study, IVF cycles with the long GnRH-a protocol and three additional injections of 0.1 mg GnRH-a on day 6 after embryo transfer did not affect the pregnancy rates [12]. Moreover, no significant increase in the clinical pregnancy rate was observed in the GnRH-a group. While Tesarik et al. [8], Qublan et al. [12] and Isik et al. [9] found GnRH-a addition to luteal phase beneficial, no significant effect was found by Ata et al. [13], Maged et al.[14] and Inamdar et al. 2012 [11].

Co-administration of GnRH-a and hCG for final oocyte maturation has been reported in several studies to improve IVF success rates in terms of the mature oocytes and pregnancy outcomes. Haas et al. [15] randomised one hundred fifty-five normal responder patients either to receive hCG or dual trigger for final oocyte maturation and reported that dual trigger group had significantly higher number of MII oocytes, top quality blastocysts, clinical pregnancy and live birth rates. In a recent meta-analysis Sloth et al. reported the effect of dual trigger in low responder patients regarding the reproductive outcome. A 1.62-fold increase in clinical pregnancy rate [OR = 1.62 (1.00–2.62), p = 0.05] and a 2.65 fold increase in live birth rate [OR = 2.65 (1.6–4.24), p = 0.0001] were observed in dual trigger group compared to hCG trigger [16]. In line of these studies, in our clinical practice we prefer dual trigger for final oocyte maturation as a routine procedure in both patients with poor and normal ovarian reserve.

The main limitations of this study were its retrospective nature and limited sample size. Due to the limited sample size we didn't make any subgroup analysis for the unexplained and low ovarian reserve groups. It would have been better to study each group separately in terms of the effect of luteal phase support with GnRH-a. However, as all the patients had fresh transfer of embryos reaching the blastocyst stage, had a single embryo transfer and had similar demographic characteristics, the results could have been slightly affected. The low pregnancy and implantation rates are attributed to the patients being the first to attempt IVF and the selection of patients with only single embryo transfer. Our study differs from other studies in two respects. First, GnRH agonist was applied together with hCG on the day of triggering oocyte maturation, which is named as 'dual trigger'. Second, GnRH agonist was given on day 5 of embryo transfer, which is named as blastocyte transfer. The present retrospective study was performed to assess the effect of an additional single dose of triptorelin, administered on the fifth day of embryo transfer in terms of chemical, clinical and live birth pregnancy rates in GnRH antagonist protocol. Findings revealed no significant difference in chemical, clinical pregnancy and live birth rates.

CONCLUSIONS

In conclusion, dual-triggered cycles with 0.25 mg triptorelin administration on the fifth day of embryo transfer in addition to routine luteal phase support may not improve the outcomes of ICSI-ET cycles.

Conflict of interest

The authors report no conflict of interests.

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