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Final oocyte maturation with two different GnRH agonists in antagonist co-treated cycles at risk of ovarian hyperstimulation syndrome

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KEY MESSAGE

GnRH agonists are effective and safe for final oocyte maturation in antagonist co-treated cycles of patients with high risk of ovarian hyperstimulation syndrome. Subcutaneous injections of triptorelin (0.2 mg) or leuprolide (1.0 mg) seem to have comparable efficacy for final oocyte maturation.

A B S T R A C T

Triptorelin 0.2 mg and leuprolide 1 mg subcutaneous injections for triggering final follicular maturation were compared in patients with a high risk for ovarian hyperstimulation syndrome (OHSS). Infertile patients treated with GnRH antagonist protocol between January 2014 and March 2016 were recruited. Patients with high serum oestradiol levels on HCG day (>3000 pg/ml) indicating a risk of OHSS consisted of the study groups (A and B). Patients with serum oestradiol levels less than 3000 pg/ml consisted of the control group (C). A single injection of 0.2 mg triptorelin, 1 mg leuprolide and 10000 IU HCG were administered for final oocyte triggering in groups A (n = 63), B (n = 74) and C (n = 131), respectively. Demographic parameters were comparable between the groups. No cases of severe or moderate OHSS occurred in any group. The clinical pregnancy rates were 31.7%, 37.8% and 32.8% in groups A, B and C, respectively. Both injections had comparable efficacy in clinical outcome and OHSS risk. Regardless of preferred drug, GnRH agonist trigger for final oocyte maturation seems to be safe for patients with high OHSS risk, and can be safely used in fresh embryo transfer cycles.

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Introduction

Mature oocytes are necessary for oocyte retrieval and fertilization; however, final oocyte maturation is the key step in IVF and intracytoplasmic sperm injection (ICSI) cycles. Final follicle maturation is triggered by HCG, which has been used as a prerequisite for oocyte fertilization for many years in IVF–ICSI cycles. Administration of HCG for final oocyte maturation, however, has resulted in supraphysiologically elevated steroid levels in the luteal phase owing to its long half-life. Hence, ovarian hyperstimulation syndrome (OHSS) risk has increased (Cerrillo et al., 2011). In addition, high oestradiol levels negatively affect endometrial receptivity and embryo quality (Simon et al., 1998; Valbuena et al., 2001).

Recently, GnRH agonists have been introduced for final oocyte maturation in GnRH antagonist down-regulated cycles (Kulikowski et al., 1995; Segal and Casper, 1992). It has been shown that GnRH agonists induce endogenous LH and FSH surges similar to natural mid-cycle LH surge with a shorter effect duration compared with exogenous HCG, which may help to reduce the risk of OHSS (Gonen et al., 1990; Kol et al., 1996). Final oocyte maturation with GnRH agonists is only applicable with ovarian stimulation cycles in which the pituitary gland remains responsive to GnRH agonist (Orvieto et al., 2006). Although GnRH agonist triggering reduces OHSS risk, it results in abnormal luteal phase. The reason for this situation is the rise of LH lasting only 24–36 h, which cannot support development and function of the corpus luteum (Engmann et al., 2008; Garcia-Velasco et al., 2010). As a result of defective luteal phase, reduced rates of implantation and live birth rates are suggested in cycles with GnRH agonist trigger (Humaidan et al., 2005). In addition to those with increased risk of OHSS, GnRH agonist trigger can also be used in normoresponder patients with extra luteal phase support. Although reduced risk has been reported, OHSS risk remains because of the extra luteal phase support by 1500 IU HCG (Humaidan et al., 2015).

To date, several studies have reported the efficacy of different types and doses of GnRH agonists, including triptorelin, buserelin, leuprolide and nafarelin administered subcutaneously or intranasally. To the best of our knowledge, however, only one non-English language study has compared the effectiveness of different GnRH agonist triggering regimens in normo-responder patients (Parneix et al., 2001). Recently, a dose-finding study reported no significant differences between triptorelin triggering with 0.2, 0.3 and 0.4 mg (Vuong et al., 2016). Similarly, in a case series, triptorelin triggering with 0.1 and 0.2 mg doses were found to have comparable efficacy (Gulekli et al., 2015). The aim of the present study was to assess the efficacy of two different GnRH agonist formulas, triptorelin acetate 0.2 mg administered subcutaneously and leuprolide acetate 1 mg adminstrered subcutaneously, in final oocyte maturation of patients with increased risk of OHSS.

Materials and methods

In this retrospective cohort study, infertile patients treated with GnRH antagonist protocol in their first ICSI cycle at a university-based infertility clinic between January 2014 (when GnRH agonists were first used for triggering in our clinic) and March 2016 were recruited. The study was approved by the Institutional Review Board of Ankara University (App. No.: 12-542-16, Date: 27 June 2016). One stimulation cycle for each patient was included in the study to prevent possible crossover bias between groups. In total, 354 patients who underwent ICSI with antagonist protocol with a starting dose of 150 IU per day during the study period were selected from the hospital database. Inclusion and exclusion crieria were applied to the data and 268 infertile patients who completed their cycle with embry transfer were found to be eligible for inclusion. Of the remaining 86 patients, nine patients with cancer had their oocytes or embryos frozen to preserve fertility, and the cycles of 77 patients were cancelled owing to non-retrieved spermatocyte in testicular sperm extraction or fertilization failure (**Figure 1**). No patients had empty follicle syndrome. The inclusion criteria were female age 18–40 years, baseline FSH level 3–15 IU/l, baseline LH level >3 IU/l, a starting dose of gonadotrophin stimulation with a dose of 150 IU/day. The exclusion criteria were secondary infertility, body mass index (BMI) over

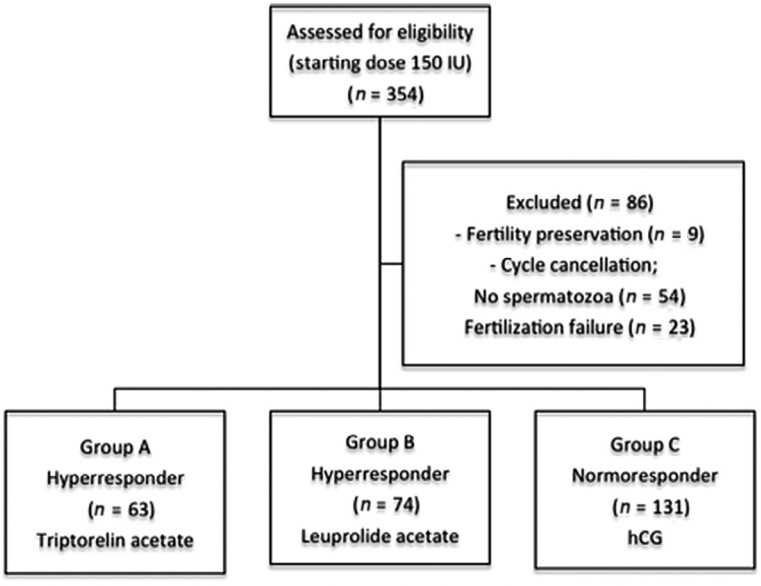

Figure 1 – Study process.

30 kg/m^2, poor response to ovarian stimulation, presence of any untreated thyroid dysfunction or hyperprolactinaemia, presence of uterine abnormality, or all the above factors. For eligible participants, all data on ovarian stimulation and clinical outcomes were extracted from the database, and patients were divided into three groups according to final oocyte trigger.

According to the ovarian stimulation policy of our centre, patients with high serum oestradiol levels (>3000 pg/ml) are not triggered by HCG to prevent OHSS. The patients with high serum oestradiol levels on HCG day (>3000 pg/ml) indicating a risk of OHSS consisted of the study groups (Groups A and B). The patients with serum oestradiol levels less than 3000 pg/ml consisted of the control group (group C). An injection of 0.2 mg triptorelin acetate (Gonapeptyl 0.1 mg, Ferring, Istanbul, Turkey), 1 mg (20 units in a tuberculin syringe of 5 mg/ml injectable solution) leuprolide acetate (Lucrin 5 mg, Abbott, Istanbul, Turkey) and 10000 IU HCG (Pregnyl; MSD, Oss, Holland) were administered for final oocyte triggering in groups A (n = 63), B (n = 74) and C (n = 131), respectively. The drug selected for ovulation stimulation in groups A and B was the primary physician's choice.

Ovarian stimulation was carried out with recombinant FSH (Gonal-F, Merck-Serono, Istanbul, Turkey) beginning from the second day of the menstrual cycle with a fixed starting dose of 150 IU/day when the antral follicle count was over 12 per ovary. Dose adjustment was carried out individually according to ovarian response. The GnRH antagonist (Cetrotide, Merck-Serono, Istanbul, Turkey) was introduced (0.25 mg/day) on the sixth day (fixed antagonist protocol) and continued throughout ovarian stimulation. When at least three follicles were 18 mm or wider, final oocyte triggering was carried out. Transvaginal ultrasonography guided oocyte retrieval was carried out 35–36 h after final oocyte trigger. Embryo transfer was carried out on the third day of oocyte retrieval. A maximum of two embryos were transferred under ultrasound guidance owing to national embryo transfer regulations (Resmi Gazete, 2010). Vaginal micronized progesterone 90 mg/day (Crinone 8% gel; Merck-Serono, Istanbul, Turkey) was administered to all patients for luteal phase support starting on the day of oocyte retrieval until the pregnancy test, and women with a positive result continued progesterone supplementation until 10 weeks of gestation. In addition, 1500 IU HCG was administered on the day of oocyte retrieval for luteal phase support in groups A and B.

The embryos were graded as A, B, and C, with the best embryos being considered those of Grade A (Gardner and Schoolcraft, 1999). Pregnancy was defined by positive serum beta-HCG levels 2 weeks after embro transfer. Clinical pregnancy was defined as the presence of heartbeat at sixth gestational week. The implantation rate was calculated separately for each woman as gestational sacs/transferred embryos x 100. The primary outcome measures were clinical pregnancy and OHSS rates.

Statistical methods

SPSS Version 21.0 (IBM Corporation, Armonk, NYC, USA) were used for data analyses. Shapiro–Wilk test was used to determine normality of distributions in samples. According to the results, parametric tests were preferred. Continuous variables were compared with one-way analysis of variance. Categorical variables were compared with chi-squared test or Fisher's exact test where appropriate. $P < 0.05$ was considered statistically significant. In the case of a statistically significant difference, a post-hoc analysis was carried out between all group pairs to define the source of statistical significance.

Table 1 – Demographic characteristics of the study and control groups.

	Group A (n = 63)	Group B (n = 74)	Group C (n = 131)
Age (years)	30.0 ± 4.6	29.7 ± 4.1	30.4 ± 5.0
Body mass index (kg/m^2)	25.2 ± 3.9	25.1 ± 3.7	24.4 ± 4.4
Duration of infertility (years)	5.9 ± 3.3	6.5 ± 3.5	7.0 ± 3.8
Cause, n (%)			
Male factor	39 (61.9)	40 (54.1)	80 (61.1)
Female factor	10 (15.9)	10 (13.5)	23 (17.6)
Unexplained	14 (22.2)	24 (32.4)	28 (21.4)
Baseline FSH (IU/ml)	6.9 ± 2.8	6.5 ± 2.0	7.5 ± 3.6
Baseline LH (IU/ml)	5.4 ± 2.5	5.5 ± 4.2	5.1 ± 2.2
Baseline oestradiol (pg/ml)	44 ± 19	52 ± 48	46 ± 50

Group A: high-responder, triggered by triptorelin; group B: high-responder, triggered by leuprolide; group C: normoresponder, triggered by HCG. There were no statistically significant differences between the groups.

Results

The groups were comparable in baseline and demographic parameters, including age, BMI, duration of infertility, cause of infertility and serum baseline hormone levels (**Table 1**).

Five patients had 25 or more oocytes collected and 21 patients had 20–24 oocytes collected within the whole study population. The cycle outcomes of study and control groups are presented in **Table 2**. Mean serum oestradiol levels, mean follicle numbers over 14 mm and over 17 mm in diameter were higher in groups A and B than in group C ($P < 0.001$). The mean numbers of retrieved oocytes and second metaphase oocytes were significantly higher in group B than in groups A and C ($P < 0.001$). The groups were found to be comparable in total amount of gonadotrophins administered, duration of stimulation, maximal endometrial thickness on day of embryo transfer, and numbers of good-quality embryos and embryos transferred.

No severe or moderate OHSS occurred in any of the groups, whereas only two mild OHSS cases were diagnosed in groups A and B, one in each. The first patient in group A was aged 22 years and her BMI was 22 kg/m^2. She was stimulated with a total dose of 2700 IU gonadotrophins and 24 oocytes were collected. Her peak oestradiol level was 4854 pg/ml. She had lower abdominal discomfort and enlarged ovaries. The second patient in group B was aged 24 years and her BMI was 20.9 kg/m^2. She was stimulated with a total dose of 3125 IU gonadotrophins and 28 oocytes were collected. Her peak oestradiol level was 5110 pg/ml. She had lower abdominal discomfort, mild nausea and vomiting and enlarged ovaries. The clinical pregnancy rates were 31.7%, 37.8% and 32.8% in groups A, B and C, respectively, as shown in **Table 3**.

Discussion

The present retrospective cohort study was conducted to assess the efficacy of two different GnRH agonists, triptorelin acetate 0.2 mg administered subcutaneously and leuprolide acetate 1 mg administered subscutaneously, for triggering final oocyte maturation in antagonist co-treated ICSI cycles with increased risk of OHSS. Although the patients administered GnRH agonist had increased risk for OHSS, the

Table 2 – Cycle characteristics of the study and control groups.

	Group A (*n* = 63)	Group B (*n* = 74)	Group C (*n* = 131)	*P*-value
Duration of stimulation (days)	10.0 ± 1.6	9.9 ± 1.2	10.4 ± 2.0	NS
Total dose of gonadotrophins (IU)	2125 ± 1192	2265 ± 712	2370 ± 918	NS
Numer of follicles wider than 14 mm on day of oocyte retrieval	6.9 ± 2.4	8.5 ± 2.9	5.3 ± 2.7	<0.001[a]
Number of follicles wider than 17 mm on day of oocyte retrieval	4.7 ± 2.4	4.9 ± 2.1	2.7 ± 1.7	<0.001[b]
Oestradiol levels on the day of trigger (pg/ml)	3332 ± 2076	3581 ± 1389	1916 ± 1328	<0.001[c]
Retrieved oocytes (*n*)	10.7 ± 6.1	14.6 ± 5.5	8.5 ± 4.8	<0.001[d]
Number of MII oocytes	8.3 ± 5.6	12.1 ± 5.3	6.8 ± 4.3	<0.001[e]
Number of Grade A embryos	3 ± 0.9	3.1 ± 1	3 ± 1.1	NS
Number of transferred embryos	1.4 ± 0.6	1.2 ± 0.4	1.3 ± 0.5	NS
Endometrial thickness on day of embryo transfer (mm)	10.3 ± 1.7	10.7 ± 2	10.8 ± 1.6	NS

Group A: high-responder, triggered by triptorelin; Group B: high-responder, triggered by leuprolide; Group C: normoresponder, triggered by HCG.
NS, not statistically significant; MII, second metaphase.
[a] Significant differences exist between all group pairs ($P_{A-B} = 0.002$; $P_{A-C} = 0.001$; $P_{B-C} < 0.001$).
[b] The significance stems from the differences between groups A and C ($P < 0.001$) and groups B and C ($P < 0.001$).
[c] The significance stems from the differences between groups A and C ($P < 0.001$) and groups B and C ($P < 0.001$).
[d] Significant differences exist between all group pairs ($P_{A-B} < 0.001$; $P_{A-C} = 0.025$; $P_{B-C} < 0.001$).
[e] The significance stems from the differences between groups A and B ($P < 0.001$) and groups B and C ($P < 0.001$).

results were comparable with normoresponder patients who were triggered with HCG. The results show that both drugs are quite comparable in clinical pregnancy and OHSS rates.

In assisted reproduction technique treatment, it is important to seek a balance between optimum ovarian stimulation and good clinical outcome with high pregnancy and minimal moderate and severe OHSS rates. During ICSI cycles, usually HCG is used for final oocyte maturation. The sustained luteotropic effect of HCG owing to its prolonged half-life results in increased risk of OHSS (Cerrillo et al., 2011). With the use of HCG for final oocyte maturation, the intravascular permeability is increased by the stimulation of vascular endothelial growth factor production, which is known as the main vascular mediator of OHSS (Cerrillo et al., 2011). Administration of GnRH agonist is a good alternative, resulting with an endogenous rise in both LH and FSH levels from the pituitary gland owing to initial flare effect similar to that of natural cycle (Gonen et al., 1990). The most significant benefit of GnRH agonist trigger is its ability to induce a quick luteolysis and therefore eliminate or reduce the risk of developing OHSS. Another important explanation for lower OHSS risk with GnRH agonist trigger is the significantly decreased vascular endothelial growth factor expression (Cerrillo et al., 2011).

According to a World Health Organization report WHO report (Hugues, 2001), OHSS is responsible for one death for every 50,000 treatment cycles, whereas the incidence of severe OHSS is 1%. To prevent severe OHSS, cycle cancellation may be preferred, but it is somewhat frustrating for patients both socially and economically. The capacity of GnRH agonist trigger for final oocyte maturation in antagonist co-treated cycles to prevent severe OHSS has been well established (Orvieto, 2015). In randomized controlled trials involving patients with high risk for OHSS, none of the patients developed OHSS in the GnRH agonist trigger group (Babayof et al., 2006; Engmann et al., 2008). On the other hand, Seyhan et al. (2013) reported 23 OHSS cases and observed five severe early OHSS cases after GnRH agonist trigger in high-risk patients. The cohort, however, was also administered additional 1500 IU HCG on the day of oocyte retrieval. Our results are concordant with other studies that show no moderate or severe OHSS cases in either high-risk group triggered with GnRH agonist. With the study by Seyhan et al. (2013), it would have been safer to avoid HCG administration and freeze all embryos in patients with large number of oocytes retrieved. The results obtained from the present study, however, suggest that GnRH agonist triggering can be more widely used in high-responder patients safely. Hence, elective freeze-all policy does not seem necessary for most GnRH agonist triggered cases.

Table 3 – Comparison of outcome measures.

	Group A (*n* = 63)	Group B (*n* = 74)	Group C (*n* = 131)
Clinical pregnancy, *n* (%)	20 (31.7)	28 (37.8)	43 (32.8)
Moderate/severe OHSS, *n* (%)	0 (0)	0 (0)	0 (0)

Group A: high-responder, triggered by triptorelin; Group B: high-responder, triggered by leuprolide; Group C: normoresponder, triggered by HCG. syndrome. There were no statistically significant differences between the groups.
OHSS, ovarian hyperstimulation.

The first published data on GnRH agonist trigger for final oocyte maturation showed lower ongoing pregnancy and live birth rates and higher miscarriage rates compared with HCG trigger (Fauser et al., 2002; Griesinger et al., 2006; Humaidan et al., 2005; Kolibianakis et al., 2005). The reason for diminished outcome was defective luteal phase in GnRH agonist triggered cycles. More recent studies, however, have reported similar pregnancy rates by using modified luteal phase protocols, including intensive luteal support, dual trigger with GnRH agonist plus low dose HCG, and GnRH agonist trigger plus 1500 IU HCG on day of oocyte retrieval for luteal phase support (Griffin et al., 2012; Humaidan et al., 2010). Although the luteal phase of the patients in our study were supported with additional 1500 IU HCG on day of occyte retrieval in GnRH agonist triggered groups, we found similar pregnancy rates with the group triggered with HCG. The luteal phase can, therefore, be rescued to enable fresh embryo transfer in GnRH agonist triggered antagonist cycles.

Although the GnRH agonist triggering is well defined for final oocyte maturation, there is still a gap in the literature about the effectiveness of different types and doses of GnRH agonists. To the best of our knowledge, our study is the first to compare triptorelin 0.2 mg and leuprolide 1 mg in English literature. Previously, Parneix et al. (2001) published in French the comparison of triptorelin, buserelin spray, buserelin subcutaneously leuprolide and nafarelin for final oocyte maturation in 231

cycles (Parneix et al., 2001). For the five main groups GnRH agonists produced shorter and inadequate luteal phases than did HCG. Pregnancy rates were similar between the agonist groups or compared with HCG group. They concluded that different modes of GnRH agonist triggering yielded comparable results. Similar to that, our results also showed comparable pregnancy and OHSS rates between triptorelin 0.2 mg and leuprolide 1 mg triggering in high-responders.

The main limitations of the present study were the retrospective nature and small sample size, especially in GnRH agonist triggering groups. For instance, the difference between triptorelin and leuprolide groups in oocyte numbers may be a reflection of different responses of each individual affecting the result in the presence of a small sample size. Also, the non-randomized case selection makes this study unlikely to be involved in future meta-analyses. The systematic exploration of individual parameters, however, and the comparison of the efficacy of drugs in a high-responder cohort may add credence to our observations. Another limitation of our study was the absence of frozen-thawed cycles in the analyses. It is plausible that inclusion of such cycles would result in better outcomes.

In conclusion, GnRH agonist triggering is an effective and safe method for final oocyte maturation in patients at high of OHSS. The triptorelin 0.2 mg and leuprolide 1 mg injections administered subcutaneously for final oocyte maturation seem to have comparable efficacy in achieving good clinical outcomes in antagonist co-treated high-responders. Whatever the type of drug, patients with high risk for OHSS can be triggered by GnRH agonists safely instead of freeze all policy.

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