Gonadotropin-releasing hormone agonist triggering is effective, even at a low dose, for final oocyte maturation in ART cycles: Case series

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Abstract

Objective: To investigate the efficacy of low-dose gonadotropin-releasing hormone (GnRH) agonist for final oocyte maturation in females undergoing assisted reproductive treatment (ART) cycles.

Material and Methods: Nine females undergoing ovarian stimulation in a GnRH antagonist protocol who received triptorelin 0.1 mg to trigger final oocyte maturation were included. Treatment outcomes of these patients were compared with those of controls, matched for age and oocyte number (n=14), who received 0.2 mg triptorelin at the same time. The luteal phase was supported with vaginal micronized progesterone and oral estradiol hemihydrate 2 mg twice daily.

Results: The mean (±) numbers of retrieved, metaphase II, and fertilized oocytes were 15.66±7.82, 14±7.28, and 10.11±5.86, respectively. The implantation and clinical pregnancy rates were 46.1% and 71.4%, respectively. Of the pregnancies, 2 were live births, 1 was a preterm birth (twins), 2 are on-going, and 2 ended as miscarriages. No case of OHSS was encountered. On comparison of the results of these patients (fresh cycles; n=7) with those of matched controls, there were no significant differences in terms of retrieved mature oocytes, implantation rates, or clinical pregnancy rates (p>0.05).

Conclusion: These findings suggest that low-dose GnRH agonist triggering has similar efficacy as standard doses in terms of retrieved mature oocytes and clinical pregnancy rates in in vitro fertilization cycles. (J Turk Ger Gynecol Assoc 2015; 16: 35-40)

Keywords: Agonist trigger, triptorelin, oocyte maturation, oocyte retrieval, pregnancy rate

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Introduction

Ovarian hyperstimulation syndrome (OHSS) is the most serious complication in in vitro fertilization (IVF) cycles, with an incidence of 3%-6% for moderate and 0.1%-2% for severe cases (1). Thus, many studies have focused on avoiding this iatrogenic complication using various strategies (2). It is well established that this syndrome almost always requires the exogenous administration of human chorionic gonadotropin (hCG) or endogenous pregnancy-derived hCG stimulation (3). However, due to its luteinizing hormone (LH) homology, extended half-life, and simple manufacturing process, hCG is an excellent trigger for final oocyte maturation (3).

Nevertheless, the introduction of gonadotropin-releasing hormone (GnRH) antagonist protocols has allowed the utilization of a GnRH agonist (a) to induce final oocyte maturation. The GnRH agonist displaces the GnRH antagonist in the pituitary gland, activating the GnRH receptor and resulting in a surge of gonadotropins (flare-up) similar to the natural midcycle surge (3). Moreover, GnRH agonist triggering has been shown to retrieve more metaphase II (MII) oocytes compared with hCG triggering (4). Kol and Humaidan hypothesized that this finding may be related to the endogenous follicle-stimulating hormone (FSH) surge elicited along with the LH surge after GnRH agonist triggering (4, 5).

Several studies have investigated the optimal dose of urinary or recombinant (r) hCG to induce oocyte maturation in IVF cycles (6, 7). The minimum optimal dose of hCG was first recommended by Abdalla et al. (8). They compared the effect of 2000-, 5000-, and 10,000-IU hCG doses for successful oocyte recovery and, as a result, recommended at least 5000 IU hCG for an adequate follicular response (8). Later, several studies concluded that the clinical outcome was similar between females receiving 5000 or 10,000 IU of urinary hCG (7). A recent study found that the optimal dose of r-hCG to induce final oocyte maturation in oocyte donors was 250 μg and that a double dose of r-hCG was not associated with a higher number of retrieved MII oocytes or higher pregnancy rates among recipients (6). In contrast, the preferred GnRH agonist doses for triggering oocyte maturation have been found to be 0.2 mg for triptorelin, 0.5 mg for buserelin, and 1

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mg for leuprolide acetate (9). Several trials have explored different doses and types of GnRHa (GnRHagonists) in terms of their induction of final follicular maturation in IUI (10-12) and egg donor cycles (13). However, there are limited data in the literature about the optimal minimum doses of GnRH agonists for inducing final oocyte maturation in IVF cycles. In this report, we present a case series to show the efficacy of a low-dose GnRH agonist (0.1 mg triptorelin) for final oocyte maturation in females undergoing assisted reproductive treatment (ART).

Material and Methods

This retrospective analysis used the data of a small case series of patients (n=9) undergoing GnRH antagonist cycles using 0.1 mg triptorelin for final oocyte maturation between March 2012 and May 2013. The study was pproved by the instutional review board and informed consent was provided by each of the couples. As there is no established dose of GnRH agonist for inducing final oocyte maturation in our center, individual attending physicians determined the dose of GnRH analog and luteal phase support according to their own preference. One of the physicians (BG) in the department preferred a lower triggering dose of GnRHa (0.1 mg triptorelin) for inducing final oocyte maturation, based on the successful results of previous IUI studies (10-12). Therefore, the current study analyzed these cases retrospectively and compared the results (fresh transfers) with a control group (n=14) on the basis of the study group.

Ovarian stimulation was initiated with recombinant FSH (Puregon; Organon, Turkey and Gonal-f; Merck Serono, Turkey) from Day 2 or 3 of the cycle and continued until the day of ovulation induction. Cycles were monitored using ultrasound scanning. A GnRH antagonist, ganirelix (Orgalutran; Organon, Turkey) or cetrorelix (Cetrotide; Merck Serono, Turkey), was administered when the leading follicle reached a maximum diameter of 14 mm. When at least two follicles had reached a diameter of 17 mm, final oocyte maturation was triggered by administering 0.1 mg triptorelin (Decapeptyl; Ferring, Turkey). Oocyte pick-up was performed 35 h and 30 min after triggering. ICSI was performed in all patients. Embryos were evaluated on the second and third days, and up to two embryos per patient were transferred. For luteal phase support, all patients received micronized progesterone 90 mg vaginally (Crinone 8% vaginal gel; Merck Serono, Turkey) and estradiol hemihydrate 2 mg orally twice daily (Estrofem tb; Novo Nordisk, Turkey).

Biochemical pregnancy was detected by measuring β-hCG levels (>10 IU/L) on Day 12 after embryo transfer. Clinical pregnancy was defined as the presence of a gestational sac with a fetal heart rate present on ultrasound at Week 6 of gestation.

Statistical analysis

Statistical Package for the Social Sciences 17 (SPSS Inc., Chicago, USA) was used for the statistical analysis. Fresh transfer cycle results were compared between the groups using Fisher's exact test and Mann-Whitney U test for non-parametric conditions. The power of the study was 0.502 (∝: 0.51). A p value of <0.05 was accepted as statistically significant.

Results

a. Cycle characteristics of Group 1, including fresh and thawed transfers (n=9)

The demographic and cycle characteristics of each patient in Group 1 (n=9) are shown in Table 1. Seven patients had fresh cycle embryo transfers. The other two patients had frozen embryos; embryo transfer was performed during a subsequent artificial cycle in these patients due to OHSS risk. Seven patients in Group 1 conceived, one of whom (case 1) had a preterm delivery of twins at Week 24 due to preterm premature rupture of membranes (PPROM), one patient had a single term delivery (case 2), one patient had a term twin delivery (case 3), two patients had an on-going pregnancy (case 4- Week 25 and case 6- Week 21), while two pregnancies ended as miscarriages (case 5 and case 9). The reproductive outcomes for these patients (including both fresh and thawed transfers) were as follows: the clinical pregnancy rate was 77.7%, the on-going pregnancy+birth rate was 55.5%, implantation rate was 52.9%, and the abortion rate was 22.2% (n=2).

b. Comparison of fresh transfers (n=7) of Group 1 with Group 2 (oocyte and age-matched control group; n=14)

Only fresh embryo transfers were included in the comparative analysis; therefore, the results of patient 3 and patient 4 in group 1 were not included in the statistical analysis. The patients' characteristics and treatment outcomes are shown in Table 2. The mean ages of patients in groups 1 and 2 were 29.89+4.48 (24-37) and 28.92±3.54 (23-36) years(y), respectively (p>0.05). There were no significant differences between the groups in mean duration of infertility, previous IVF attempts, duration of stimulation, or total dose of gonadotropins required (p>0.05). There were also no significant differences in the mean number of aspirated follicles, mean number of retrieved oocytes, or mean number of metaphase II oocytes between the groups (p>0.05). Immature oocytes (MI) were significantly more numerous in group 2 than in group 1 (p<0.05). Fertilization rates were similar in both groups (72% in group 1 and 73% in group 2). The nean number of embryos was 10.11±5.86 (4-21) in group 1 and 10.79±3.14 (7-18) in group 2. The numbers of transferred embryos were 1.85±0.37 (1-2) and 1.36±0.49 (1-2) in groups 1 and 2, respectively (p<0.05). There were no significant differences between the groups in implantation rate (46.1% vs. 57.8%), clinical pregnancy rate (71.4% vs. 57.1%), and on-going pregnancy rates (42.8% vs. 42.8%) (p>0.05). There was no case of OHSS in any patient in either group.

Discussion

The major goal of studies in the field of assisted reproductive technologies is to improve the live birth rate while minimizing complications and the cost of treatment. Previous reports have claimed that GnRH agonist triggering in GnRH antagonist cycles is a new and effective modality for the most feared complication of controlled ovarian stimulation, OHSS (14). It has now been demonstrated that the flare-up effects of GnRH agonists with modified luteal support yield similar conceptual results as hCG in fresh IVF cycles (15, 16).

Table 1. Demographic and cycle characteristics of patients in Group 1 (n=9)

Case No	**1**	**2**	**3**	**4**	**5**
Age (y)	30	32.5	25	31	
BMI (kg/m^2)	28	33.5	22	24	
Cause of Infertility	Male factor+ tubal factor	PCOS	PCOS	PCOS+ endometriosis	Tubal factor
Previous IVF attempts	3	1	2	2	0
Total dose of gonadotropin (IU)	1650	1650	900	900	3150
Retrieved oocytes (n)	13	18	32	22	9
Metaphase II oocytes (MII)	13	15	30	20	9
Immature oocytes (MI-GV)	0	3	2	2	0
Fertilization rate (%)	84	66	70	90	88
2PN (n)	11	10	21	18	8
Day 3 embryos frozen (n)	6	3	13	12	0
Grade 1 embryos (n)	5	4	13	12	5
Embryos transferred (n)	2	2	Total freeze FET(2)	Total freeze FET(2)	2
IVF outcome	Pregnancy (twin) Preterm delivery (23rd week)	Live birth (single)	Live birth (twin)	Pregnancy-ongoing 22nd week-single)	Pregnancy (7th week missed abortus)
Case No	6	7	8	9	
Age (y)	25	25	34	33	
BMI (kg/m^2)	33	31.2	33.2	22.8	
Cause of infertility	Male factor	Male factor	Tubal factor+ Male factor	PCOS	
Previous IVF attempts	1	1	7	1	
Total dose of gonadotropin (IU)	1650	2875	3850	800	
Retrieved oocytes (n)	10	15	16	6	
Metaphase II oocytes (MII)	9	14	10	6	
Immature oocytes (MI-GV)	1	1	6	0	
Fertilization rate (%)	44	71	50	83	
2PN (n)	4	10	5	5	
Day 3 embryos frozen (n)	0	2	0	0	
Grade 1 embryos (n)	2	5	3	4	
Embryos transferred (n)	2	2	1	2	
IVF outcome	Pregnancy-ongoing (16th week-single)	Negative	Negative	Pregnancy (6th week missed)	

BMI: body mass index; IVF: in vitro fertilization; 2 PN: 2 pronucleus; n:number y: year; MI: metaphase I; GV: germinal vesicle; IU: international unit.

Although there are many reports about the optimal dose of hCG for inducing final oocyte maturation, there are limited data about the minimal optimal doses to trigger using GnRH agonists in IVF cycles (6, 7, 17, 18). Most previous studies have reported successful oocyte maturation with 0.2-0.3 mg triptorelin, 0.5 mg buserelin, and 1 mg leuprolide acetate (13). A similar clinical outcome was observed with 0.1 mg of triptorelin and 10,000 IU hCG in a GnRH antagonist protocol in a study that was presented during the 19th ESHRE meeting but has not yet been published (19). In a recent study of oocyte maturation using 0.1, 0.3, and 0.5 mg triptorelin, ovulation occurred in all IUI cycles (17). As there is no established dose of GnRH agonists for the induction of final oocyte maturation in IVF cycles, we hypothesized that lower doses of GnRHa may be sufficient for triggering. Herein, we report successful oocyte maturation using a lower dose of triptorelin acetate in a small case series.

As described in many reports, the main problem in GnRHa-triggered antagonist cycles is luteal phase support rather than

Table 2. Comparison of matched 0.1 and 0.2 mg triptorelin-triggered groups for fresh transfer

Variable	Group 1 (n=7)*	Group 2 (n=14)	p
Age (y)	29.89±4.48 (24-37)	28.92±3.54 (23-36)	0.256
BMI (kg/m^2)	27.78±4.98 (22-33.5)	26.45±3.98 (21-32)	0.289
Duration of infertility (y)	5±3.42 (1-9)	4.86±3.2 (1-14)	0.787
Number of Previous IVF attempts	2.0±0.68 (1-7)	1.43±0.64 (1-3)	0.306
Basal FSH (mIU/mL)	6.43±1.29 (4.1-8.1)	5.78±1.39 (3.2-8.0)	0.387
Stimulation (days)	11±4.82 (7-23)	10.38±1.39 (7-13)	0.631
Total dose of FSH (IU)	1936.11±1101.20 (800-3850)	1727.8±755.45 (750-3250)	0.481
Aspirated follicles (n)	17.55±7.71 (11-35)	18.34±6.87 (9-30)	0.704
Retrieved oocytes (n)	15.66±7.82 (6-32)	17.04±4.0 (10-26)	0.513
Retrieved oocytes per aspirated follicles (%)	89	92	0.906
Metaphase II oocytes (MII)	14±7.28 (6-30)	14.0±3.50 (9-22)	0.980
Immature oocytes (MI-GV)	1.66±1.12 (0-6)	3.04±2.32 (0-6)	<0.05
Fertilization rate (%)	72	73	0.270
2PN (n)	10.11±5.86 (4-21)	10.79±3.14 (7-18)	0.717
Embryos transferred (n)	1.85±0.37 (1-2)	1.36±0.49 (1-2)	<0.05
Implantation rate per cycle n (%)	6/13 (46.1)	11/19 (57.8)	0.471
Clinical pregnancy rate per cycle n (%)	5/7 (71.4)	8/14 (57.1)	0.290
Ongoing pregnancy + birth rate per cycle n (%)	3/7 (42.8)	6/14 (42.8)	0.433
Abortion rate per cycle n (%)	2/7 (28.6)	2/14 (14.2)	0.517
OHSS rate per cycle n (%)	0/7(0)	0/14 (0)	ns

*: Seven patients including fresh transfers.
IVF: in vitro fertilization; n: number: year; 2 PN: 2 pronucleus; MI: metaphase I; GV: germinal vesicle; IU: international unit; OHSS: ovarian hyperstimulation syndrome.

oocyte maturation, since the decrease in gonadotropins that are released from the pituitary results in corpus luteum deficiency and a defective luteal phase (20). Do lower triggering doses of GnRH agonists negatively affect the luteal phase? In a recent report, an inadequate luteal phase was observed in 34.4% of the non-conceptional cycles of patients receiving triptorelin 0.1 mg to trigger ovulation in IUI cycles; however, increasing or repeating triptorelin did not restore the luteal phase or the pregnancy rate (17). Shalev et al. (11) compared the effects of 10,000 IU hCG and 0.1 mg triptorelin on ovulation after clomiphene citrate treatment. Interestingly, midluteal progesterone concentrations (>10 ng/mL) and the mean luteal phase duration were normal in both groups. Also, there were no significant differences in pregnancy and abortion rates between groups, which may have been related to the different dynamics at midcycle in clomiphene-stimulated cycles due to a direct hypothalamic effect (10, 21). Parneix et al. (12) also investigated the effect of different doses and modes of application of GnRH agonists for triggering ovulation, finding that although ovulation occurred in all groups, shorter and inadequate luteal phases were seen in all groups. According to these findings, higher doses and different modes of GnRH agonists for triggering do not appear to improve the luteal phase in non-IVF cycles.

Standard luteal phase support after GnRH agonist triggering has been reported to be associated with lower conception rates due to corpus luteum dysfunction (22). Therefore, intensive luteal phase supplementation is recommended to achieve optimal conception rates (22). Also, since excellent pregnancy rates were reported in patients undergoing frozen embryo transfer using GnRHa suppression protocols, Engmann et al. (22) suggested that LH may not be critical for implantation. Therefore, aggressive luteal support may be another beneficial approach in agonist trigger cycles. Engmann et al. (23) reported excellent implantation and on-going pregnancy rates with intensive luteal support using intramuscular progesterone daily and estradiol patches on alternate days. Although intramuscular administration (IM) of progesterone results in higher serum levels, some studies also support the use of vaginal progesterone gel (24). In our study, all patients received micronized estradiol hemihydrate 4 mg orally combined with progesterone 90 mg vaginally twice daily for luteal support.

The main aim of this report was to demonstrate the effectiveness of lower doses of agonists to trigger final oocyte maturation, rather than pregnancy rates. Indeed, the rate of retrieved oocytes per follicle (89%) and fertilization rate (71%) seem to support the use of lower doses of GnRH agonists in clinical practice. These results also highlight the inadvertent administration of a lower dose (i.e., one instead of two ampoules) to the patients. Finally, clinicians should recognize that the cost of treatment can be reduced by using the minimum optimal dose of GnRH agonist for triggering.

Another important aspect of agonist-triggered cycles is the incidence of empty follicle syndrome (EFS). The incidence of EFS has been reported as 0.6%-3.5% in GnRHa trigger cycles, which is similar to that reported (0.1%-3.1%) after an hCG trigger (12, 19, 25-29). Therefore, EFS is not an inherent and exclusive problem to the GnRHa trigger (25) but could be related to human error, abnormalities in the *in vivo* biological activity of some batches of commercially available GnRHa, hypothalamic dysfunction, or GnRH receptor mutations (23, 26, 28-30). Elucidating the relationship between lower doses of GnRHa and EFS will require further studies including a larger number of patients. However, in our case series, there were no EFS and no reduced number of retrieved oocytes. Also, the association between BMI and the required GnRHa dose is controversial. Although Kummer et al. (25) demonstrated that a higher BMI corresponded to less of an increase in LH and lower post-trigger progesterone level, they found that BMI did not predict the oocyte yield. However, it is possible that the excess subcutaneous tissue in obese patients interferes with the absorption of medication. Only three patients in the current study were obese, and there was no reduced number of mature oocytes or EFS in these patients. However, determining the optimal GnRHa dose according to BMI will require further research.

The major limitation of our study was definitely the low number of patients. Therefore, the power of the study was relatively low to make a precise comparative analysis. However, the aim of this study was to report the effectiveness of low-dose GnRH agonist triggering in these cases.

In conclusion, the current study attempted to diagnose the effectiveness of low-dose GnRH agonist triggering in oocyte maturation. Our results suggest that 0.1 mg triptorelin acetate effectively induces final oocyte maturation in IVF cycles. However, as this was a small case series, larger randomized controlled studies are needed to determine the optimal dose for GnRH agonist triggering.

Ethics Committee Approval: *Ethics committee approval was received for this study from the ethics committee of Instutional Review Board.*

Informed Consent: *Written informed consent was obtained from patients who participated in this study.*

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