Reproductive Medicine; *Endocrinology and Infertility*

Comparison of hCG Versus Gonadotropin-Releasing Hormone Agonist to Induce Oocyte Maturation in Assisted Reproductive Technology Cycles: A Retrospective Cohort Study

Gulay BEYDILLI NACAK[1], Elif TOZKIR[1], Enis OZKAYA[1], Ebru COGENDEZ[1], Fatih KAYA[1]

Istabul, Turkey

ABSTRACT

OBJECTIVE: To compare some cycle characteristics and outcomes using a protocol consisting of a GnRH agonist trigger or hCG trigger after cotreatment with GnRH antagonist.

STUDY DESIGN: Thirty-three patients under 35 years of age with polycystic ovarian syndrome, polycystic ovarian morphology, or previous high response who underwent ovulation trigger by GnRH agonist trigger and 132 patients under 35 years of age with the polycystic ovarian syndrome, polycystic ovarian morphology, or previous high response who underwent ovulation trigger by hCG for IVF treatment. Patients were non-randomly assigned to an ovarian stimulation protocol consisting of either GnRH agonist trigger after cotreatment with GnRH antagonist (study group) or hCG trigger after antagonist protocol (control group).

RESULTS: The positive pregnancy test was obtained in 70 women in the control group whereas in 13 cases in the study group (*p*=0.161). No case in the study group needed hospitalization whereas there were 15 cases in the control group who were required to be hospitalized due to ovarian hyperstimulation related symptoms (*p*=0.04).

CONCLUSIONS: The use of a protocol consisting of a GnRH agonist trigger after GnRH antagonist cotreatment and freeze-all strategy reduces the risk of ovarian hyperstimulation syndrome in high-risk patients undergoing IVF without affecting pregnancy rates.

Keywords: GnRH agonist, GnRH antagonist, In vitro fertilization, Ovarian hyperstimulation syndrome, Polycystic ovary morphology, Polycystic ovary syndrome

Introduction

Ovarian hyperstimulation syndrome (OHSS) is an iatrogenic complication of controlled ovarian hyperstimulation (COH), which may result in severe morbidity and rarely mortality (1). Although there has been significant progress over the years in assisted reproductive technology, there is currently no effective strategy to address this disorder (2). One of the best strategies for the prevention of OHSS is the identification of high-risk patients and the use of an appropriate ovarian stimulation protocol. High-risk patients include young women with polycystic ovary syndrome (PCOS) (3,4) and patients with a history of previous high response to gonadotropins. It has been suggested that the administration of a GnRH agent to induce the final oocyte maturation may lead to a reduction in the risk of OHSS (5,6). This is due to the shorter half-life of endogenous LH fluctuation and subsequent suppression of the pituitary, leading to early luteolysis and decreased luteal phase steroidal concentration (7). On the other hand, there is insufficient data in the literature in terms of cycle characteristics and success following the agonist trigger.

The aim of this study was to compare some cycle characteristics and outcome of cycles using a protocol consisting of GnRH agonist trigger after cotreatment with GnRH antagonist or hCG trigger in antagonist protocols

[1] Department of Obstetrics and Gynecology, Health Sciences University Zeynep Kamil Women and Children's Diseases Training and Research Hospital, Istanbul, Turkey

Address of Correspondence: Enis Ozkaya
Department of Obstetrics and Gynecology, Health Sciences University Zeynep Kamil Women and Children's Diseases Training and Research Hospital, 34668 Üsküdar, Istanbul, Turkey
enozkaya1979@gmail.com

Quick Response Code:	Access this article online
	Website: www.gorm.com.tr e- mail: info@gorm.com.tr
	DOI:10.21613/GORM.2020.1034

How to cite this article: *Beydilli Nacak G. Tozkir E. Ozkaya E. Cogendez E. Kaya F. Comparison of hCG Versus Gonadotropin-Releasing Hormone Agonist to Induce Oocyte Maturation in Assisted Reproductive Technology Cycles:A Retrospective Cohort Study. Gynecol Obstet Reprod Med. 2021;27(2):143-149*

Material and Method

This was a retrospective cohort study involving patients undergoing In vitro fertilization (IVF) treatment at the ART (assisted reproductive technology) center of Health Sciences University Zeynep Kamil Women and Children's Health Training and Research Hospital. The subjects were recruited for a period of 48 months between January 2015 and January 2019. This study was conducted in accordance with the Declaration of Helsinki. Approval for this study was obtained from the Institutional Review Board (2016/74).

Participants: Patients were enrolled in the study if they fulfilled the following criteria: age 23–35 years at the time of screening, normal early follicular phase serum FSH concentration (<10.0 IU/L), and undergoing their first cycle of IVF with either PCOS or PCOM (polycystic ovary morphology) or undergoing a subsequent cycle with a history of high response in a previous IVF cycle. Polycystic ovary syndrome was defined according to the Rotterdam consensus guidelines (8), and the evaluation of PCOM was based on the international consensus definitions (9). Previous high responders were patients who either developed OHSS underwent coasting, or had a cycle canceled for risk of OHSS in a previous cycle.

Consecutive thirty-three patients under 35 years of age with polycystic ovarian syndrome, polycystic ovarian morphology, or previous high response undergoing IVF who underwent ovulation trigger by GnRH agonist and again consecutive 132 patients under 35 years of age with polycystic ovarian syndrome, polycystic ovarian morphology, or previous high response undergoing IVF who underwent ovulation trigger by hCG were included in this study.

Treatment Protocol: For all participants, a gonadotropin-secreting hormone antagonist protocol was used for IVF/ICSI. On the second day of the menstrual cycle, the daily follicle-stimulating hormone (rFSH; Gonal-F, Merck-Serono, Geneva, Switzerland) was initiated. The dose used ranged from 150 IU to 300 IU and was determined by the baseline clinical characteristics of each patient. Mean follicular growth was monitored by two-dimensional transvaginal sonography every 2-3 days. The daily dose of rFSH was adjusted from day 5 of stimulation according to the ovarian response. Antagonist (Cetrorelix, Merck-Sereno, Geneva, Switzerland) was administered at a dose of 0.25 mg/day when the follicular size reached 12 mm. When the follicular size reached 18 mm, 250 microg recombinant human chorionic gonadotropins (hCG; Ovitrelle, Merck-Sereno, Geneva, Switzerland) was administered subcutaneously and follicular puncture was performed 34-36 hours later. Then, 8% vaginal progesterone gel (Crinone gel 8%; Merck-Sereno, Geneva, Switzerland) was applied twice daily. ICSI was performed for each oocyte obtained by follicular puncture. According to the developmental characteristics of the embryo, the elective transfer of an embryo was performed at the cleavage (day 3) or blastocyst (day 5) stage. Serum levels of the hCG (β-hCG) G-subunit were measured after 2 weeks. The patient was considered to have successful implantation if it was equal to or greater than normal levels (5 IU/L) during pregnancy. Patients in the study group, final oocyte maturation was triggered by administering 0.2 mg triptorelin (Decapeptyl; Ferring, Turkey) approximately 12 hours after the last dose of ganirelix.

Transvaginal ultrasound–directed oocyte retrieval was performed 35 hours after GnRH or hCG administration. Embryo transfer was performed 72 to 76 hours after oocyte retrieval. Supernumerary multicellular embryos of good quality or blastocysts were then cryopreserved on days 3 and/or 5 respectively in the group of women who underwent agonist trigger. The embryos were graded according to the criteria described by Cummins et al. (10). Timing and endometrial preparations for Frozen embryo transfers were determined according to the article by Mackens et al (11). Estradiol hemihydrate 2 mg 3 times/day was administered orally under transvaginal monitorization with 2-3 days intervals until the endometrial thickness reached 9-14 mm. Then intravaginal progesterone gel was administered. The duration of luteal phase supplementation was determined according to the day of the frozen embryo (day of frozen embryo+1).

Outcome Variables: The primary efficacy endpoint was the incidence of OHSS and the secondary endpoint pregnancy rate. Additional points of interest were the number of oocytes taken, the ratio of mature oocytes obtained, the rate of fertilization. OHSS was diagnosed by Golan et al. (12). All patients were brought back after 7 days of oocyte uptake (mid-luteal phase) and their symptoms, findings, sonographic and laboratory evidence were evaluated.

Statistical analyses were performed using Statistical Package for Social Sciences (Publication 17.0; SPSS, Chicago, IL). When appropriate, chi-square or Fisher exact tests were used for categorical variables. Independent samples t-test was used for continuous variables with normal distribution and the Mann-Whitney U test was used for data with no normal distribution. All p values quoted are bilateral and values below .05 are taken to indicate statistical significance.

Results

Comparison of groups in terms of some demographic characteristics was summarized in table I which showed similar age, BMI and duration of infertility ($p>0.05$, Table I). The primary infertility rates were similar between the two groups (81.8% vs. 78.8%, $p>0.05$). The rates of patients with PCOS were also similar between the two groups (50.8% vs. 51.5%, $p>0.05$). Again, the rates of patients with previous IVF trials were similar between groups with and without agonist trigger (32.6% vs. 33.4%, $p>0.05$). Baseline ovarian reserve tests were similar between groups ($p>0.05$, Table II). The coasting procedure was required in 4 (12.1%) cases with agonist trig-

ger, on the other hand, 50 (37.9%) cases in the group with hCG trigger ($p=0.005$). Oocyte fertilization rates did not differ between the two groups (94.7% vs. 93.9%, $p>0.05$). Different embryo grade rates were comparable between the two groups ($p>0.05$, Table III). Among 33 women who un-

derwent agonist trigger, freeze all strategy was indicated for 21 cases, whereas among 132 women in the control group freeze all strategy was preferred in 10 cases ($p<0.001$). All of the parameters representing the cycle characteristics were similar between groups ($p>0.05$, Table IV). Positive preg-

Table I: *Comparison of groups in terms of some demographic characteristics*

	Trigger	n	Mean	Std. deviation	p value
Age (Years)	Agonist	33	29.7	4.01	
	hCG	132	30.1	4.4	0.6 (MWU)
BMI (kg/m^2)	Agonist	17	24.7	5.2	
	hCG	51	23.1	3.1	0.09
Duration of infertility (months)	Agonist	33	44.2	35.5	
	hCG	132	53.5	40.8	0.3 (MWU)

BMI: Body mass index, MWU: Mann Whitney-U

Table II: *Baseline ovarian reserve tests were similar between groups*

	Trigger	n	Mean	Std. deviation	p value
FSH (mIU/mL)	hCG	132	5.150	1.3310	
	Agonist	33	5.034	1.4141	0.5
Estradiol (pg/mL)	hCG	132	40.91	15.726	
	Agonist	33	45.67	17.996	0.2 (MWU)
AFC	hCG	132	18.32	6.014	
	Agonist	33	19.06	6.210	0.5 (MWU)

FSH: Follicle stimulating hormone, AFC: Antral follicle count, MWU: Mann Whitney-U

Table III: *Different embryo grade rates were comparable between the two groups*

		Embryo Grade				p value
		1	2	3	4	
Trigger	hCG	81	20	2	21	
		65.3%	16.1%	1.6%	16.9%	
	Agonist	19	4	2	6	0.5
		61.3%	12.9%	6.5%	19.4%	
Total		100	24	4	27	
		64.5%	15.5%	2.6%	17.4%	

hCG: Human chorionic gonadotropin

Table IV: *All of the parameters of representing the cycle characteristics were similar between groups*

	Trigger	n	Mean	Std. deviation	p value (MWU)
Starting Gonadotropin Dose (U)	hCG	132	208.7	58.6	
	Agonist	33	212.8	58.6	0.7
Total Gonadotropin Dose (U)	hCG	132	1856.4	909.8	
	Agonist	33	1931.4	727.5	0.2
Day 5 Estradiol (pg/mL)	hCG	132	800.9	502.6	
	Agonist	33	825.3	566.9	0.9
Duration of Induction	hCG	132	8.8	1.6	
	Agonist	33	9.1	2.05	0.3
Peak Estradiol (pg/mL)	hCG	132	4272.09	1964.8	
	Agonist	33	4060.5	1161.9	0.5
# of total oocytes	hCG	132	12.2	5.7	
	Agonist	33	13.8	6.08	0.2
# of mature oocytes	hCG	132	9.6	4.9	
	Agonist	33	11.2	5.2	0.1
Fertilization rate (%)	hCG	131	90	20	
	Agonist	33	94	24.2	0.9

#: number, MWU: Mann Whitney-U

nancy tests were obtained in 70 women in the control group whereas in 13 cases in the study group (p=0.161). There was a single case with mild OHSS in the study group whereas, in the control group, 19 OHSS cases were observed (p=0.07). No case in the study group needed hospitalization whereas 15 cases in the control group required hospitalization (p=0.04).

Discussion

In this study, we aimed to compare some characteristics and outcomes of cycles using a protocol consisting of GnRH agonist trigger after cotreatment with GnRH antagonist or hCG trigger in antagonist protocols. Our comparison revealed that the use of a protocol consisting of GnRH agonist trigger after GnRH antagonist cotreatment and freeze-all strategy reduces the risk of OHSS in high-risk patients undergoing IVF without affecting pregnancy rates.

To date, various strategies have been proposed for the prevention of OHSS in high-risk patients, but none have been shown to eliminate the risk of OHSS (2). Previous studies have shown that the induction of oocyte maturation with the GnRH agonist after GnRH antagonist co-treatment can potentially prevent the development of OHSS (5,6,13). On the other hand, there is insufficient data in the literature in terms of cycle characteristics and success following agonist trigger. The OHSS inhibition mechanism after the GnRH agonist trigger was not fully investigated. Administration of a single dose of the GnRH agonist causes an endogenous rise of both FSH and LH, resulting in the induction of the final stages of oocyte maturation, after bedtime with the GnRH antagonist (14,15). The shorter half-life of the internal LH fluctuation and subsequent suppression of the pituitary and withdrawal of LH support for corpora lutea may lead to early luteolysis (7). The GnRH agonist has been advocated since 1989 to trigger oocyte maturation and ovulation (16). However, it is not widely accepted and widely used for various reasons. First, GnRH fell in favor in the 1990s due to the widespread use of agonist desensitization protocols; Second, one of the major disadvantages of the GnRH agonist trigger is the weaker induction of luteal phase and consequently impaired steroid circulation (14,15). In fact, recent publications showed that the GnRH agonist trigger may result in impaired implantation and ongoing pregnancy rates in normal responders (17-19). In a previous study, two groups of patients who were assigned to receive either GnRHa trigger (n=98 cycles) or hCG trigger (n=99 cycles) for ovulation trigger were compared for intrauterine insemination (IUI) cycle outcome. No difference was found in ovulation rates in either group receiving GnRHa or hCG trigger for ovulation. Biochemical and clinical pregnancy rates were higher in group with hCG trigger (28.3% and 23.2%) versus GnRHa (14.3% and 13.3%) (p=0.023, and p=0.09, respectively). However, this study showed that after adjusting for body mass index and infertility duration, there was no difference in clinical pregnancy rates between the two groups (p=0.163). The authors of this study concluded that the use of the GnRHa to trigger ovulation in patients undergoing ovulation induction may be considered in patients treated with IUI (20). In our study population cases who underwent the GnRHa trigger was required to be directed to the "Freeze-all" strategy. The "Freeze-all" strategy was questioned in the literature. The "Freeze-all" policy has been proposed for the general IVF population; (21) there are important concerns that need to be taken into consideration although the initial studies and a meta-analysis supported the use of "Freeze-all" policy for the general IVF population (22,23), recent evidence from larger randomized clinical trials in more specific subpopulations does not support the general use of "Freeze-all" policy (24-26) moreover, some authors reported higher early pregnancy loss rates related to frozen-thawed cycles, (27) as well as a higher incidence of adverse obstetrical and perinatal outcomes, (28) which might be induced by either the endometrial priming protocol prior to embryo transfer or the cryo-technique itself. In contrast, in patients with OHSS risk, the benefits from the "Freeze-all" policy may already outweigh all the reported risks (29). Hence, the clinician has the possibility to counterbalance benefits and risks in the OHSS risk patient by using either a fresh cycle with GnRHa trigger and modified luteal phase support or turning directly to "Freeze-all" policy. Another possible drawback of the GnRH trigger was suggested to be increased risk for empty follicle syndrome. Some studies have been published indicating this issue for example in the previous study, clinicians aimed to investigate the incidence of empty follicle syndrome (EFS) occurring in gonadotropin-releasing hormone agonist-induced IVF cycles in women with the polycystic ovarian syndrome and GnRH antagonist protocol. Following an ovulation trigger by GnRHa in the IVF cycle of 279 PCOS patients; the incidence of EFS following GnRHa was reported to be 3.3%. Among these cases 88.8% (8/9) of EFSs had false empty follicle syndrome; Six of 9 cases were given a rescue trigger and a very high level of embryo transfer was reported in the FET cycle of 3 of these cases. The authors of this study concluded that, although small, the majority of EFS was false and can be effectively recovered and lead to reasonable positive results (30). Further investigations have been conducted to put forth this issue; Griesinger et al. reported that EFS was seen in only one patient in a study of 51 cases after the freeze. In the same study, the live birth rate after the first freeze-thaw embryo transfer was reported as 5.9% in the slow freeze group and 19.4% in the vitrification group. In three cases, moderate OHSS (5.9%) was diagnosed and an early onset severe OHSS developed in one case (2%). The OHSS criterion was the Golan classification, and as a result of the study, the authors concluded that cryopreservation was an effective and safe method after triggering with agonist, although there was a severe early-onset OHSS case (31). These data showed us that empty follicle syndrome did not seem to be a drawback following the GnRHa trigger.

As we emphasized with this study, the GnRHa trigger has

been considered to be an OHSS preventive measure. Several data have been presented on this issue; Fatemi et al. reported two severe cases of OHSS in the GnRH antagonist protocol in 2014 after the GnRH agonist without any hCG for luteal phase support. Based on these cases, GnRH, FSH and LH receptor mutations and the emergence of a clinical connection between the emergence and severity of OHSS and need to be aware that OHSS cannot be completely eliminated despite all the measures taken (32). In a retrospective study by Koren et al. in 2018, ovulation was triggered with the GnRH agonist instead of the classical hCG trigger in IVF patients with an E2 level of ≥3,000 pg/mL. In this study, the authors applied the "Freeze-all" decision when the number of oocytes collected was 20 and above; on day 3 after oocyte collection, single bolus rescue hCG was administered for fresh embryo transfers. The authors found clinical pregnancy rate and OHSS rates similar in both groups at the end of the study and reported that both strategies seemed to be effective and safe, especially the upper limit of 20 oocytes was safe to implement a rescue hCG strategy (33). A study similar to ours was conducted in 2018 by Hwang et al. None of the 40 IVF patients who underwent GnRH analog trigger and the "Freeze-all" were reported to have moderate or severe ovarian hyperstimulation syndrome (0%). At the end of the study, the authors reported the clinical pregnancy rate after frozen-thawed embryo transfer as 57.5% per cycle, and the cumulative rate of pregnancy after three embryos was 75.0% (34). In that study, the long-acting corifollitropin alpha was used for ovarian stimulation and followed by leuprolide acetate for ovulation trigger. Finally, Stormlund et al. are conducting a multicenter randomized, controlled, double-blind study with 424 normoresponder IVF patients aged 18 to 39 years from Denmark and Sweden. The results of fresh blastocyst (single) transfer will be compared with hCG triggers in gonadotropin-induced cyclic cases. The primary outcome of the study was reported to be as ongoing pregnancy rates and the results have not been reported yet (35).

The major disadvantage of this study was retrospective nature and small sample size. Cases were selected in a consecutive manner to overcome possible bias during patient selection. Further studies are needed to show live birth rates and newborn outcome following GnRH trigger.

In conclusion, the use of a protocol consisting of GnRH agonist trigger after GnRH antagonist cotreatment and the "Freeze-all" strategy reduces the risk of OHSS in high-risk patients undergoing IVF without affecting cycle characteristics and pregnancy rates.

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