Received: 29 September 2021 | Accepted: 1 February 2022

DOI: 10.1002/rmb2.12448

Reproductive Medicine and Biology

WILEY

ORIGINAL ARTICLE

The novel oral gonadotropin-releasing hormone receptor antagonist relugolix is a new option for controlled ovarian stimulation cycles

Shinnosuke Komiya[1,2] | Tomoko Tsuzuki-Nakao[1] | Yoshiko Asai[2] | Tomoko Inoue[2] | Yoshiharu Morimoto[2] | Hidetaka Okada[1]

[1]Department of Obstetrics and Gynecology, Kansai Medical University Graduate School of Medicine, Osaka, Japan

[2]HORAC Grand Front Osaka Clinic, Osaka, Japan

Correspondence
Hidetaka Okada, Department of Obstetrics and Gynecology, Kansai Medical University Graduate School of Medicine, 2-5-1 Shin-machi, Hirakata, Osaka 573-1010, Japan.
Email: hokada@hirakata.kmu.ac.jp

Abstract

Purpose: Relugolix is an oral gonadotropin-releasing hormone antagonist (GnRHant), which was first introduced in 2019. This study investigated the effects of the conventional injectable GnRHant formulation and this new oral GnRHant formulation on controlled ovarian stimulation (COS) cycles.

Methods: Relugolix was administered in 126 cycles and conventional GnRHant injection was administered in 658 cycles (controls). The follicle stimulation was performed by an antagonist method, and for final oocyte maturation, recombinant human chorionic gonadotropin (rHCG), or gonadotropin-releasing hormone agonist (GnRHa), or both (dual trigger) were selected. The number of retrieved oocytes was counted and then they were evaluated for subsequent development up to cleavage stage.

Results: The number of retrieved oocytes which was the primary outcome of this research was affected by the combination of GnRHant type and the final oocyte maturation agent. The combination of relugolix and a GnRHa trigger showed a significantly lower number of retrieved oocytes ($p < 0.001$) than the other combinations.

Conclusions: Relugolix is a new option for COS cycles, but should be carefully combined with the final maturation agent.

Clinical trial approval: This study was conducted after approval by the Medical Corporation Sankeikai Institutional Ethics Committee (approval number: 2019-34).

KEYWORDS
fertilization in vitro, infertility, oocyte retrieval, reproductive techniques, assisted, sperm injections, intra-cytoplasmic

1 | INTRODUCTION

The number of infertility treatment cycles have been increasing every year due to various social reasons. In 2019, 458 101 in vitro fertilization (IVF) or intra-cytoplasmic sperm injection (ICSI) embryo transfer cycles were performed in Japan.[1] Although fertility treatment depends on the patients' condition, it often starts with timed intercourse or intrauterine insemination.[2] These basic infertility treatments are aimed at single follicular development. If a woman fails to conceive for several months after basic infertility treatment

and has an active plan to have a child, it is necessary to take the help of assisted reproductive technologies (ART).[3]

The most notable difference between basic and ART treatments is the strategy of follicular stimulation and the associated increase in the number of visits to the clinic. Follicular stimulation with follicle-stimulating hormone (FSH)/human menopausal hormone (HMG) injections for multiple follicular development requires daily visits to the clinic for injections or self-injection.[4] Many women who try fertility treatment are at an age where they have a busy career and can manage only a limited number of daily visits to the clinic. Therefore, they often opt for self-injection.

Patients tend to view injections as being unavoidable because daily injections are essential for fertility treatment, but the act of injecting medicine by pointing a needle at oneself is highly invasive. Especially in people with needle phobia, the inability to self-inject makes balancing career and fertility treatments difficult because of the requirement of daily visits to the hospital. Therefore, a minimally invasive and effective oocyte retrieval protocol is desirable to reduce the physical, mental, and social burdens of infertility patients.

In controlled ovarian stimulation (COS) cycles in Japan, non-injection options, such as clomifene citrate, cyclofenil, and letrozole, are available, but completely injection-free COS cycles are rare. A long or short protocol requires more units of gonadotropin than an antagonist protocol because the pituitary function is suppressed by the downregulation effect of long-term administration of gonadotropin-releasing hormone agonist (GnRHa) products. Additionally, human chorionic gonadotropin (HCG) injection must be used for final maturation.[5,6] However, in an antagonist protocol, the number of injections increases because of the injectable gonadotropin-releasing hormone receptor antagonist (GnRHant; i.e., cetrorelix acetate or ganirelix acetate) in the second half of the COS cycle, but a GnRHa preparation (buserelin acetate nasal spray) can be selected for the final maturation instead of HCG injection.[7]

Although oral GnRHant preparations such as elagolix, relugolix, and linzagolix have been available for treating endometriosis and fibroids, there are no reports of them being used in COS cycles. Relugolix (RELUMINA®) was the first oral selective GnRHant to be launched in Japan in January 2019.[8] Although relugolix is usually used to improve symptoms due to uterine fibroids, theoretically, its pharmacological effects as GnRHant could be applied to COS cycles. By switching from an injectable to an oral GnRHant, a less invasive follicle-stimulating protocol is possible. Therefore, we designed a clinical study to test the hypothesis that IVF/ICSI results of COS protocols using relugolix and conventional injectable GnRHant preparations are similar.

2 | MATERIALS AND METHOD

2.1 | Study design, setting, and inclusion criteria

We used an open-label, non-random, prospective case–control study design. Participants were provided unbiased information about commonly used drugs for the COS cycle (FSH, HMG, cetrorelix acetate, ganirelix acetate, and buserelin acetate) and relugolix. They were assigned to receive two different interventions; GnRHant with either cetrorelix acetate or ganirelix acetate (control group) or with relugolix (study group) based on their choice. Since masking was not possible, the study was conducted as an open trial. The intervention period was from January 2019 to August 2020. The inclusion criteria were as follows: (1) patients who were scheduled for oocyte retrieval in which the COS cycle was with an antagonist protocol, and (2) patients who could provide written consent. No specific exclusion criteria were set.

2.2 | Treatment selection and cancellation

A total of 785 COS cycles in the antagonist protocol were performed during the inclusion period, and relugolix was used in 127 (16.2%) cycles. One case (0.8%) of study group and five cases (0.8%) of control group were canceled owing to extremely low number of developing follicles. Finally, 779 COS cycles were analyzed. Multiple COS cycles by the same patient were included because the primary outcome was the number of retrieved oocytes. Selection of the participants, and the final oocyte maturation agent, is shown in Figure 1.

2.3 | Antagonist protocol

A COS cycle with daily injections of follitropin alpha (genetic recombination) (Gonalf®, Merck Biopharma Co., Ltd.) or HMG (HMG for injection [FERRING]®, Ferring Pharmaceuticals Co., Ltd.) and GnRHant administration was defined as the antagonist protocol. FSH or HMG injections were started on days 2–4 of the menstrual cycle. The initial dose was set at 150–300 IU/day at the discretion of the attending physician on the basis of serum anti-Müllerian hormone (AMH) levels, the antral follicle count, and ovarian responses in previous COS cycles. The GnRHant for pituitary suppression was started when the maximum follicular diameter reached 14 mm. When multiple follicles reaching ≥18 mm were observed, final oocyte maturation was triggered, and FSH/HMG and GnRHant agents were not administered on the trigger day. Oocyte retrieval was performed at 35–36 h post the trigger.

2.4 | Study and control groups

In the study group, 40 mg/day of relugolix (RELUMINA®; ASKA Pharmaceutical Co., Ltd.) was used as the GnRHant preparation. In the control group, cetrorelix acetate (Cetrotide®; Merck Biopharma Co., Ltd.) 0.25 mg/day or ganirelix acetate (GANIREST®; MSD KK a subsidiary of Merck & Co. Inc.) 0.25 mg/day was used. In this study, GnRHant preparation (relugolix, cetrorelix acetate, or ganirelix acetate) was administered at the same time as FSH/HMG injections.

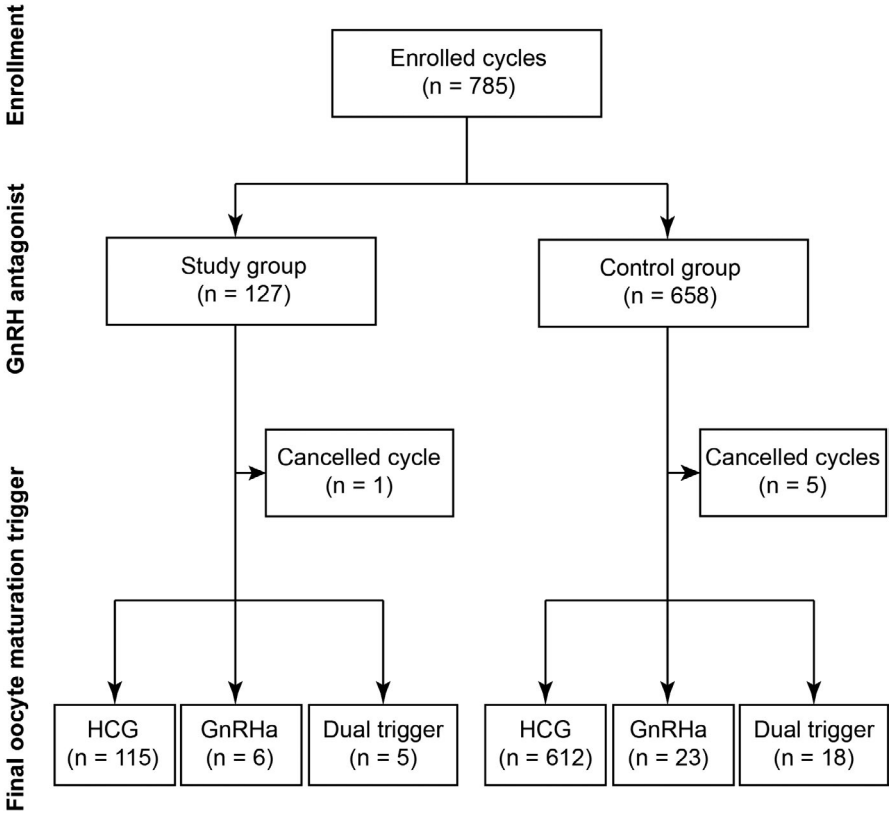

FIGURE 1 Flow diagram of participants in the study

2.5 | Final oocyte maturation

A total of 600 μg of buserelin acetate as the GnRHa (Suprecur® nasal solution 0.15%; MOCHIDA Pharmaceutical Co., Ltd.), 250 μg of chorionadotropin alpha (genetic recombination; Ovidrel® Syringe for subcutaneous injection; Merck Biopharma Co., Ltd.), or a dual trigger was selected depending on the case. Our policy was to choose a GnRHa for patients with a high risk of ovarian hyper-stimulation syndrome (OHSS), but the final trigger was determined by the attending physician on the basis of the follicle size and physical status on the trigger day. A dual trigger was selected for patients with a history of a low maturation rate with a GnRHa or recombinant HCG trigger alone.[9]

2.6 | Outcomes

The primary outcome was the number of retrieved oocytes. Secondary outcomes were the number of oocytes in metaphase II (M II) and the number of good quality cleavage stage embryos (Veeck's classification: grades 1–3). Information on adverse events was also recorded as an indicator of safety.

2.7 | Statistical analysis

As there were no previous studies on relugolix in IVF/ICSI cycles, all the patients from the inclusion period were recruited for the study. The analysis was performed on an intention to treat (ITT) basis.[10] Missing data were complemented by the multiple imputation method.[11] Comparisons between the two groups were made using the *t*-test and Fisher's exact test, and each index was expressed as the mean and standard deviation (SD). Regression analysis was performed using the generalized linear model method.[12] Finally, comparison of regression coefficients was performed using analysis of covariance (ANCOVA). All analyses were performed with R software (version 3.6.0; https://www.r-project.org). All tests of significance were two sided and $p < 0.05$ was considered statistically significant.

3 | RESULTS

3.1 | Background and COS information

Age, AMH, pregnancy history, cause of infertility, serum estradiol (E_2), progesterone (P_4), and luteinizing hormone (LH) levels on the day of the final oocyte maturation trigger, the total number of units of FSH/HMG preparation and the total number of days of GnRHant agents used during COS cycle, the final oocyte maturation agent, and the fertilization method were compared between the study and control groups (Table 1). There were no significant differences in the patients' background and COS information.

3.2 | Serum E_2 levels and the number of retrieved oocytes

Initially, we predicted that serum E_2 levels and the number of retrieved oocytes would be positively correlated. However, especially in the study group, the number of retrieved oocytes tended to decrease when E_2 levels exceeded 3000–5000 pg/ml. To accurately

assess the number of retrieved oocytes, the 779 cycles were divided into the low E_2 group (<3000 pg/ml) and the high E_2 group (≥3000 pg/ml), and the patients' background data were compared (Table 2). To examine the effect of age, AMH, serum E_2 levels, relugolix, and the final oocyte maturation agent on the number of retrieved oocytes, multiple regression analysis was performed. The possibility of multicollinearity was examined by variance inflation factor (VIF), and the VIF of all variables was less than 2, indication that multicollinearity did not occur. The *F* test for coefficient of determination was F (6, 772) = 71.31 ($p < 0.001$). The partial regression coefficients for age (95% CI [−0.24 to −0.13]) and serum E_2 levels (95% CI [0.0017–0.0022]) were significant at the 5% level ($p < 0.001$).

3.3 | Crossover effect between a GnRHant and final oocyte maturation

To evaluate the crossover effect of the GnRHant preparation and the final oocyte maturation agent, we compared the number of retrieved oocytes between the study and control groups by the final oocyte maturation agent (Figure 2). The regression lines of the study and control group were compared when the objective value was the number of retrieved oocytes using ANCOVA. When HCG was used for the final maturation, no interaction was found between the regression lines (F (1, 724) = 1.16, $p = 0.28$), and there was no significant difference between the regression lines (F (1, 723) = 0.07, $p = 0.79$). When GnRHa was used for the final maturation, no interaction was found between the regression lines (F (1, 26) = 3.20, $p = 0.09$), but a significant difference was found between the regression lines (F (1, 25) = 15.31, $p < 0.001$). When dual trigger was used for final maturation, no interaction was found between the regression lines (F (1, 20) = 1.28, $p = 0.27$), and there was no significant difference between the regression lines (F (1, 19) = 0.47, $p = 0.50$).

The scatter plot and the regression lines of the dual, GnRHa, and HCG trigger groups with the numbers of MII oocytes and cleavage stage embryos as the objective variables are shown in Figure S1.

TABLE 1 Background characteristics of the patients and information of COS cycles

Variables	Control group (*n* = 653)	Study group (*n* = 126)	*p* value
Age (years)	37.8 ± 4.7	38.6 ± 4.1	0.09
AMH (ng/ml)	2.7 ± 1.7	2.9 ± 2.3	0.24
History of gravidity (*n*)	0.09 ± 0.3	0.09 ± 0.3	0.93
History of parity (*n*)	0.03 ± 0.2	0.04 ± 0.2	0.68
Cause of infertility			0.94
Combined factor (%)	456 (69.8)	90 (71.4)	
Male factor (%)	54 (8.3)	13 (10.3)	
Tubal factor (%)	25 (3.8)	4 (3.2)	
Ovulation factor (%)	17 (2.6)	3 (2.4)	
Uterine factor (%)	11 (1.7)	2 (1.6)	
Unexplained (%)	90 (13.8)	14 (11.1)	
Trigger day serum E_2 (pg/ml)	1828.5 ± 1254.3	1865.3 ± 1536.9	0.77
Trigger day serum P_4 (pg/ml)	1.1 ± 4.0	0.6 ± 0.8	0.25
Trigger day serum LH (mIU/ml)	4.1 ± 4.1	3.3 ± 5.0	0.07
Total units of FSH/HMG preparation (IU)	1822.6 ± 617.9	1821.4 ± 587.2	0.99
Total days of GnRHant use (days)	2.4 ± 1.0	2.5 ± 0.9	0.21
Premature ovulation (%)	0 (0.0)	0 (0.0)	1.00
Final oocyte maturation trigger			0.60
HCG (%)	612 (93.7)	115 (91.3)	
GnRHa (%)	23 (3.5)	6 (4.8)	
Dual trigger (%)	18 (2.8)	5 (4.0)	
Fertilization method			0.35
Conventional (%)	136 (20.8)	21 (16.7)	
ICSI (%)	517 (79.2)	105 (83.3)	

Note: Values are presented as mean ± standard deviation or *n* (%). The *p* values were calculated using the *t*-test or one-way analysis of variance.
Abbreviations: AMH, anti-Müllerian hormone; E_2, estradiol; P_4, progesterone; LH, luteinizing hormone; FSH, follicle-stimulating hormone; HMG, human menopause gonadotropin; GnRHant, gonadotropin-releasing hormone antagonist; COS, controlled ovarian stimulation; HCG, human chorionic gonadotropin; GnRHa, gonadotropin-releasing hormone agonist; ICSI, intra-cytoplasmic sperm injection.

TABLE 2 Comparison of the patients' background and detail of COS cycles between the low E_2 group and the high E_2 group

Variables	Low E_2 group ($n = 663$)	High E_2 group ($n = 116$)	p value
Age (years)	38.4 ± 4.6	35.5 ± 3.6	<0.001
AMH (ng/ml)	2.4 ± 1.4	4.9 ± 2.2	<0.001
History of gravidity, *n*	0.1 ± 0.3	0.1 ± 0.4	0.86
History of parity, *n*	0.03 ± 0.2	0.1 ± 0.3	0.09
Cause of infertility			0.62
Combined factor (%)	460 (69.4)	86 (74.1)	
Male factor (%)	61 (9.2)	6 (5.1)	
Tubal factor (%)	24 (3.6)	5 (4.3)	
Ovulation factor (%)	18 (2.7)	2 (1.7)	
Uterine factor (%)	10 (1.5)	3 (2.6)	
Unexplained (%)	90 (13.6)	14 (12.1)	
Trigger day serum E_2 (pg/ml)	1412.0 ± 716.1	4249.4 ± 1274.8	<0.001
Trigger day serum P_4 (pg/ml)	1.0 ± 4.0	0.8 ± 0.6	0.67
Trigger day serum LH (mIU/ml)	4.0 ± 4.4	3.5 ± 3.5	0.22
Total units of FSH/HMG preparation (IU)	1837.4 ± 619.4	1736.4 ± 567.6	0.10
Total days of GnRHant use (days)	2.4 ± 1.0	2.5 ± 1.0	0.22
Premature ovulation (%)	0 (0.0)	0 (0.0)	1.00
Final oocyte maturation trigger			<0.001
HCG (%)	628 (94.7)	99 (85.3)	
GnRHa (%)	16 (2.4)	13 (11.2)	
Dual trigger (%)	19 (2.9)	4 (3.4)	
Fertilization method			0.05
Conventional (%)	142 (21.4)	15 (12.9)	
ICSI (%)	521 (78.6)	101 (87.1)	
Use of relugolix (%)	104 (15.7)	22 (19.0)	0.45

Note: Serum E_2 levels <3000 (pg/ml) on the trigger day were categorized as the low E_2 group and those ≥3000 (pg/ml) were categorized as the high E_2 group. Values are presented as mean ± standard deviation or *n* (%). The *p* values were calculated using the *t*-test or one-way analysis of variance.
Abbreviations: AMH, anti-Müllerian hormone; E_2, estradiol; P_4, progesterone; LH, luteinizing hormone; FSH, follicle-stimulating hormone; HMG, human menopause gonadotropin; GnRHant, gonadotropin-releasing hormone antagonist; COS, controlled ovarian stimulation; HCG, human chorionic gonadotropin; GnRHa, gonadotropin-releasing hormone agonist; ICSI, intra-cytoplasmic sperm injection.

3.4 | Adverse events

Although the cause was unclear, three (2.3%) patients in the study group were switched to cetrorelix acetate because of insufficient LH suppression. Seven (1.1%) patients in the control group were switched to relugolix because of solid local reactions (redness and pain) at the injection site. All analyzed cases were analyzed on ITT basis rather than per-protocol basis because of the possibility of further heterogeneity in patient background and because ITT basis analysis reflects the actual situation when applied in daily practice.[10] As a sub-analysis, case/control comparisons based on a per-protocol basis (excluding 10 cases in which administered GnRHant preparation was changed) are shown in Tables S1 and S2. Additionally, there were no cases of a premature rise in progesterone levels.[13,14] In the study group, two (1.6%) patients had fatigue and mild headache, but there were no severe conditions. Twenty-three (18.3%) patients in study group and 125 (19.2%) patients in control group were diagnosed with mild or worsened OHSS (no significant difference). There were also no hospitalization cases of apparent intra-abdominal hemorrhage, severe ovarian hemorrhage, intra-abdominal infection, or severe OHSS, although there were a few cases of minor vaginal wall bleeding during oocyte retrieval.

3.5 | Sub-analysis on per-protocol basis

To show the effect of each GnRHant preparation directly, we additionally analyzed the interaction between GnRHant and final oocyte maturation on a per-protocol basis. The regression lines for the comparison of case and control groups by final oocyte maturation agent were also done on a per-protocol basis. The results of the *F*-test as well as the ITT basis are summarized in Table 3. There was no interaction between the regression lines in either condition, but as in the analysis on the ITT basis, there was a significant difference between

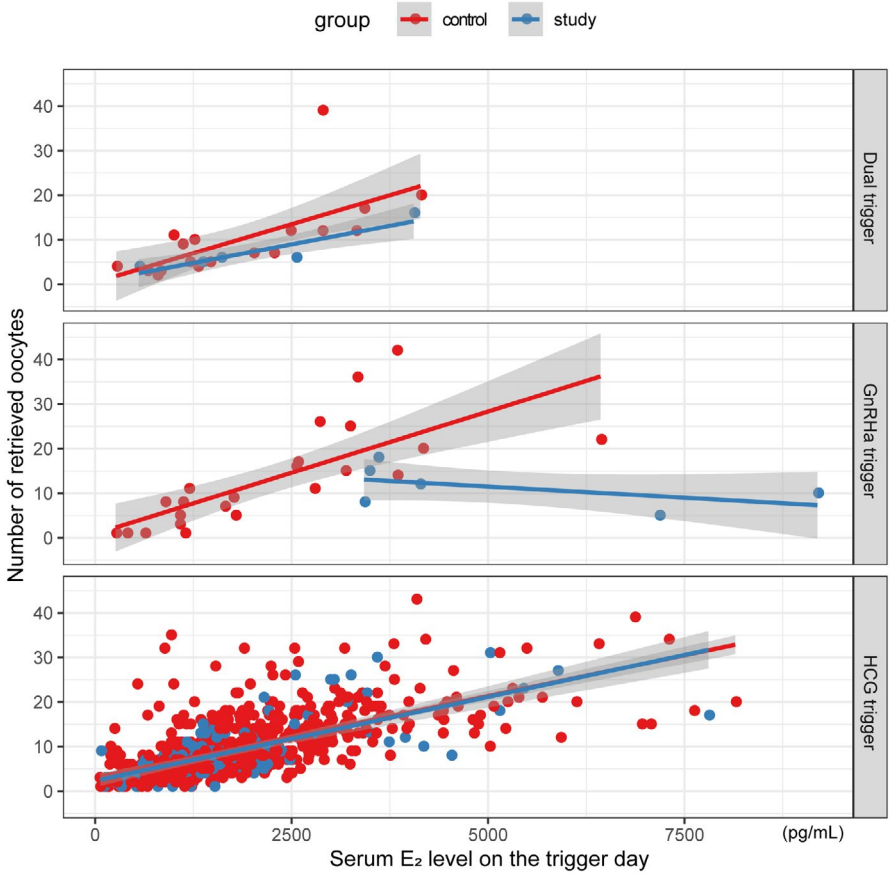

FIGURE 2 Scatter plot comparing the number of retrieved oocytes by the final maturation agent. Regression analysis was performed using the generalized liner model

TABLE 3 Analysis of Covariance (ANCOVA) for the impact of the number of retrieved oocytes adjusted for E_2 value and the use of relugolix with ITT and per-protocol basis

		ANCOVA			
Final maturation	**Variables**	**Type III sums of squares**	**df**	***F* value**	***p* value**
ITT basis					
Dual trigger	E_2	634.7	1	16.6	<0.001
	Relugolix	49.1	1	1.28	0.27
GnRHa	E_2	675.1	1	7.75	0.01
	Relugolix	279.2	1	3.20	0.09
HCG	E_2	15369.6	1	601.1	<0.001
	Relugolix	29.7	1	1.16	0.28
Per-protocol basis					
Dual trigger	E_2	634.7	1	16.6	<0.001
	Relugolix	49.1	1	1.28	0.27
GnRHa	E_2	675.1	1	7.75	0.01
	Relugolix	279.2	1	3.20	0.09
HCG	E_2	15322.3	1	596.3	<0.001
	Relugolix	33.7	1	1.31	0.25

Abbreviations: ANCOVA, analysis of covariance; df, degrees of freedom; E_2, estradiol; GnRHa, gonadotropin-releasing hormone agonist; HCG, human chorionic gonadotropin.

the regression lines when GnRHa was used for final maturation (F (1, 25) = 15.3, $p < 0.001$). There was no significant difference between the regression lines when HCG or dual trigger was used for final maturation.

4 | DISCUSSION

This is the first report to show the effect of the oral GnRHant preparation relugolix, in antagonist protocol for COS. This can reduce the

need for self-injections which is a burden for patients in COS cycles. Theoretically, relugolix is expected to have the same pituitary function-suppressing effect as other injectable GnRHant agents, such as cetrorelix acetate or ganirelix acetate. Although relugolix has been used in many facilities during oocyte retrieval cycles, there is only one published report of the effects of relugolix on oocyte retrieval outcomes and is limited to mild stimulation cycles.[15] To clarify the effect of relugolix on oocyte retrieval outcomes, this study was conducted to examine the relationship between serum E_2 levels on the trigger day and the number of retrieved oocytes.

This study showed that the oocyte retrieval performance was not affected by relugolix when HCG or a dual trigger was selected as the final oocyte maturation trigger. However, when a GnRHa trigger was used in high E2 cases to reduce the risk of severe OHSS, the number of retrieved oocytes considerably diminished (Figure 2). The cause of this reduction in the number of retrieved oocytes using the relugolix cycle may be partly due to the mechanism of different final oocyte maturation agent.

The comparison of the number of retrieved oocytes between the GnRHa-triggered study group ($n = 6$) and the control group ($n = 23$) showed a statistically clear difference in the regression line (Figure 2), although the number of cases was small. At the time of this analysis, it was predicted that attempting GnRHa triggering in the study group would likely be detrimental to patient benefit, and further patient aggregation was judged to be ethically inappropriate.

HCG acts similar to an LH surge by binding to the LH-HCG receptor. HCG has an alpha subunit in common with LH and a beta subunit with 81% amino acid sequence equivalence as LH.[16,17] The primary feature of HCG is that it has a long half-life, which may prolong its luteotropic effect.[18,19] Therefore, while sufficient maturation can be expected, HCG triggering is a high-risk factor for OHSS.[20]

A GnRHa induces an endogenous LH surge using a flare-up effect before downregulation. Additionally, a GnRHa can induce a biphasic LH surge for 24–36 h, which is shorter than the physiological LH surge.[21] The physiological LH surge is triphasic and lasts 48 h or longer. Therefore, when GnRHa triggering is performed, the total amount of gonadotropin released from the pituitary gland is reduced, which decreases the risk of developing OHSS.[22]

Relugolix is a selective antagonist of the human pituitary GnRH receptor and inhibits the secretion of gonadotropins from the pituitary gland.[8] In a pharmacokinetic study, a single oral dose of 40 mg of relugolix before breakfast was administered to premenopausal female volunteers ($n = 12$), and the half-life was reported to be 45.42 h.[8] In a phase I study in male volunteers, the half-life of relugolix ranged from approximately 36 to 65 h.[23] Because the half-life of relugolix is long, the COS schedule in this study was designed to avoid using a GnRHant on the day of the final oocyte maturation trigger. Despite these adjustments, LH levels on the trigger day in the study group were found to be lower than those in the control group (3.3 vs. 4.1 mIU/ml, $p = 0.07$). The prolonged inhibitory effect of relugolix on pituitary function may have resulted in low LH levels.

In the HCG trigger or dual-trigger cycle, the number of retrieved oocytes in the study group was similar to that in the control group owing to its long half-life and strong LH surge-like maturation effect. However, in the GnRHa trigger cycle, the inhibitory effect of relugolix on pituitary function was considered to be relatively strong against the LH surge by GnRHa.

In this study, GnRHa maturation was selected for patients with a high number of developing follicles and symptoms of OHSS. In spite of the expectation of a higher number of retrieved oocytes in OHSS patients, maximum of 18 oocytes were retrieved (Figure 2), and the maximum number of cleavage stage embryos was only 3 (Figure S1), which impaired patient satisfaction and presented a major clinical problem.

In patients with less risk of OHSS, the use of relugolix is a good option to reduce the invasiveness of self-injection during COS because an HCG trigger or dual trigger can be selected and the IVF/ICSI outcome is not affected. However, the use of relugolix is not recommended in patients in whom the risk of OHSS is expected to be high (patients with a history of OHSS, high serum AMH levels, and high antral follicle count) and a GnRHa may be used as the final oocyte maturation trigger. In this situation, the acquisition of stable, mature oocytes is a priority (cases of onco-fertility or medical fertility preservation) and the ovarian response during COS is unpredictable (first IVF/ICSI cases).

There were no significant differences in the total number of FSH/HMG units used or the duration of GnRHant administered during the COS cycles (ITT basis: $p = 0.99$, $p = 0.21$, respectively; per-protocol basis: $p = 0.81$, $p = 0.23$, respectively). Therefore, the difference in the cost for a COS cycle would be due to the difference in the selling price of GnRHant preparations at each institution.

Blinding in this study was not possible because of the different dosage forms. Therefore, the fact that our study was not a randomized trial is a limitation of the study design. However, because the incompatibility of relugolix and the GnRHa trigger was confirmed even after adjusting for the patients' background, the results of this study could be replicated in randomized trials. In addition, the number of cases in the GnRHa-triggered study group ($n = 6$) and the control group ($n = 23$) was small, and it cannot be denied that the two cases with high E_2 in the GnRHa-triggered study group may have been PCOS with high risk of empty follicle syndrome. Although we considered accumulating additional cases to address selection bias, we did not add new cases in this study because the Ethics Committee disapproved. In this study, a blastocyst was not included as an outcome for the following reasons: (1) the method of determining the COS cycle was arbitrarily chosen on the basis of past follicular development and ovarian reserve; (2) in low AMH cases, the expected number of retrieved oocytes was low, and the COS cycle was planned for cleavage stage vitrification; and (3) in the antagonist protocol, a COS cycle for two-step (cleavage stage + blastocyst) vitrification was planned as our routine procedure, and the embryos

were arbitrarily selected to be cultured until a blastocyst stage depending on the embryonic development status.

Other limitations of this study include the possible application of the results to other populations besides the Japanese. In Japan, GnRHa triggers are often used in the form of nasal spray, whereas injectable formulations are more common in other countries. Additionally, relugolix is currently approved only in the USA and Japan. Therefore, additional studies on the use of relugolix during COS cycles in other countries are required in the future.

In an efficacy and safety study of IVF/ICSI treatment cycles in Japanese women, daily once oral administration of 40 mg relugolix from the time when the dominant follicle reached 14 mm to the final oocyte maturation trigger-enabled oocyte retrieval. There was no premature ovulation or severe adverse event. However, when relugolix was used in a COS cycle with a GnRHa trigger, the oocyte retrieval results were inferior. These results suggest that oral relugolix is a new option for COS cycles, but caution should be used for its indications.

ACKNOWLEDGMENTS

We are grateful to all doctors and staff of HORAC Grand Front Osaka Clinic for medical examination services. We thank Ellen Knapp, PhD, from Edanz (https://jp.edanz.com/ac), and Manjula Brahmajosyula, PhD, from Sankeikai Medical Corporation, for editing the English text of the draft of this manuscript.

DISCLOSURES

Conflict of interest: The authors declare that they have no conflict of interest. *Human rights statements and informed consent*: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and its later amendments. *Approval by ethics committee*: This study was conducted after approval by the Medical Corporation Sankeikai Institutional Ethics Committee (approval number: 2019-34). Written informed consent was obtained from all patients for being included in the study. *Clinical trial registry*: UMIN000045607.

ORCID

Shinnosuke Komiya https://orcid.org/0000-0002-5587-7809
Hidetaka Okada https://orcid.org/0000-0002-7932-6999

REFERENCES

1. ART Registry of Japan, 2019. Japan Society of Obstetrics and Gynecology. 2021. https://plaza.umin.ac.jp/~jsog-art/ Accessed October 21, 2021
2. Gunn DD, Bates GW. Evidence-based approach to unexplained infertility: a systematic review. *Fertil Steril*. 2016;105:1566-1574 e1. doi:10.1016/j.fertnstert.2016.02.001
3. Farquhar C, Marjoribanks J. Assisted reproductive technology: an overview of Cochrane Reviews. *Cochrane Database Syst Rev*. 2018;8:CD010537. doi:10.1002/14651858.CD010537.pub5
4. Nakagawa K, Oba M, Ehara K, et al. Clinical outcomes of assisted reproductive technology treatment by using a self-injection of recombinant human chorionic gonadotropin as the final maturation trigger. *Reprod Med Biol*. 2018;17:203-208. doi:10.1002/rmb2.12095
5. Pantos K, Meimeth-Damianaki T, Vaxevanoglou T, Kapetanakis E. Prospective study of a modified gonadotropin-releasing hormone agonist long protocol in an in vitro fertilization program. *Fertil Steril*. 1994;61:709-713. doi:10.1016/s0015-0282(16)56650-3
6. Yokota Y, Yokota M, Yokota H, Ishikawa Y, Sato S, Ariki Y. Relationship between follicular fluid hormone levels, embryo quality, and maternal age during in vitro fertilization after the short or long protocol with a gonadotropin releasing hormone agonist. *Reprod Med Biol*. 2003;2:165-169. doi:10.1111/j.1447-0578.2003.00042.x
7. Byrd S, Itskovitz J, Chillik C, Hogden GD. Flexible protocol for administration of human follicle-stimulating hormone with gonadotropin-releasing hormone antagonist. *Fertil Steril*. 1992;57:209-214. doi:10.1016/S0015-0282(16)54803-1
8. Relugolix MA. First global approval. *Drugs*. 2019;79:675-679. doi:10.1007/s40265-019-01105-0
9. Haas J, Bassil R, Samara N, et al. GnRH agonist and hCG (dual trigger) versus hCG trigger for final follicular maturation: a double-blinded, randomized controlled study. *Hum Reprod*. 2020;35:1648-1654. doi:10.1093/humrep/deaa107
10. Sedgwick P. Intention to treat analysis versus per protocol analysis of trial data. *BMJ*. 2015;350:h681. doi:10.1136/bmj.h681
11. Sterne JAC, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ*. 2009;338:b2393. doi:10.1136/bmj.b2393
12. Nelder JA, Wedderburn RWM. Generalized liner models. *J R Stat Soc Ser A Stat Soc*. 1972;135:370-384. doi:10.2307/2344614
13. Lu X, Khor S, Zhu Q, et al. Decrease in preovulatory serum estradiol is a valuable marker for predicting premature ovulation in natural/unstimulated in vitro fertilization cycle. *J Ovarian Res*. 2018;11:96. doi:10.1186/s13048-018-0469-x
14. Lawrenz B, Melado L, Fatemi H. Premature progesterone rise in ART-cycles. *Reprod Biol*. 2018;18:1-4. doi:10.1016/j.repbio.2018.01.001
15. Nakao K, Kuroda K, Horikawa T, et al. Therapeutic effects of an oral gonadotropin-releasing hormone receptor antagonist, relugolix, on preventing premature ovulation in mild ovarian stimulation for IVF. *Reprod Med Biol*. 2021;21:1-9. doi:10.1002/rmb2.12422
16. Kessler MJ, Reddy MS, Shah RH, Bahl OP. Structures of N-glycosidic carbohydrate units of human chorionic gonadotropin. *J Biol Chem*. 1979;254:7901-7908.
17. Kessler MJ, Mise T, Ghai RD, Bahl OP. Structure and location of the O-glycosidic carbohydrate units of human chorionic gonadotropin. *J Biol Chem*. 1979;254:7909-7914.
18. Damewood MD, Shen W, Zacur HA, Schlaff WD, Rock JA, Wallach EE. Disappearance of exogenously administered human chorionic gonadotropin. *Fertil Steril*. 1989;52:398-400. doi:10.1016/s0015-0282(16)60906-8
19. Schmitt EJ, Diaz T, Barros CM, et al. Differential response of the luteal phase and fertility in cattle following ovulation of the first-wave follicle with human chorionic gonadotropin or an agonist of gonadotropin-releasing hormone. *J Anim Sci*. 1996;74:1074-1083. doi:10.2527/1996.7451074x
20. Youssef MAFM, Van der Veen F, Al-Inany HG, et al. Gonadotropin-releasing hormone agonist versus HCG for oocyte triggering in antagonist-assisted reproductive technology. *Cochrane Database Syst Rev*. 2014;10:CD008046. doi:10.1002/14651858.CD008046.pub4
21. Hoff JD, Quigley ME, Yen SS. Hormonal dynamics at midcycle: a reevaluation. *J Clin Endocrinol Metab*. 1983;57:792-796. doi:10.1210/jcem-57-4-792
22. Mourad S, Brown J, Farquhar C. Interventions for the prevention of OHSS in ART cycles: an overview of Cochrane reviews. *Cochrane Database Syst Rev*. 2017;1:CD012103. doi:10.1002/14651858.CD012103.pub2

23. MacLean DB, Shi H, Faessel HM, Saad F. Medical castration using the investigational oral GnRH antagonist TAK-385 (Relugolix): phase 1 study in healthy males. *J Clin Endocrinol Metab*. 2015;100:4579-4587. doi:10.1210/jc.2015-2770

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Komiya S, Tsuzuki-Nakao T, Asai Y, Inoue T, Morimoto Y, Okada H. The novel oral gonadotropin-releasing hormone receptor antagonist relugolix is a new option for controlled ovarian stimulation cycles. *Reprod Med Biol*. 2022;21:e12448. doi:10.1002/rmb2.12448