Received: 13 October 2017 | Accepted: 4 February 2018

DOI: 10.1002/rmb2.12095

ORIGINAL ARTICLE

WILEY Reproductive Medicine and Biology

Clinical outcomes of assisted reproductive technology treatment by using a self-injection of recombinant human chorionic gonadotropin as the final maturation trigger

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Abstract

Purpose: To evaluate the efficacy and safety of self-injections of the prefilled recombinant human chorionic gonadotropin (r-hCG) in a syringe in assisted reproductive technology (ART) treatment for the maturation trigger (MT), as compared to self-injections of conventional hCG and intranasal administration of gonadotropin-releasing hormone agonist (GnRH-a).

Methods: Between January and April, 2017, 396 patients who underwent oocyte retrieval were recruited. Of these, 396 patients were classified into three groups, according to the types of MT: (1) the urinary human chorionic gonadotropin (u-hCG) group that consisted of patients who had a self-injection of u-hCG (n = 127); (2) the GnRH-a group that received nasal administration of GnRH-a (n = 159); and (3) the r-hCG group that had a self-injection of r-hCG (n = 110). Several ART outcomes were evaluated.

Results: The mature oocyte retrieval rate was not different between the u-hCG, r-hCG, and GnRH-a groups and the fertilization and cleavage rates were similar between the three groups. The clinical pregnancy rates did not significantly differ between the GnRH-a group and the u-hCG group; however, it was significantly lower in the GnRH-a group, compared to the r-hCG group. No difference was observed in the incidence of moderate or more severe ovarian hyperstimulation syndrome among the three groups.

Conclusion: The self-injection of the prefilled r-hCG is a favorable MT for ART patients.

KEYWORDS

gonadotropin-releasing hormone analog, maturation trigger, ovarian hyperstimulation syndrome, recombinant human chorionic gonadotrophin, urinary human chorionic gonadotropin

1 | INTRODUCTION

Oocyte retrieval is an essential procedure in assisted reproductive technology (ART) treatment. Following oocyte retrieval, the retrieved oocytes should be manipulated to enable fertilization by insemination (conventional insemination or intracytoplasmic sperm injection [ICSI]). Insemination usually is performed after several hours of culture, following oocyte retrieval. Consequently, it is preferable that oocyte retrieval be conducted in the morning because a fertilization check has to be done 14-18 hours after insemination. Therefore, the final maturation trigger is usually given at night two days before oocyte retrieval. There are two methods of giving the final maturation trigger for oocyte retrieval in ART treatment in Japan, i.m. or s.c. injection of human chorionic gonadotrophin (hCG) or the intranasal administration of gonadotropin-releasing hormone agonist (GnRH-a), each of which has advantages and disadvantages. The use of hCG has advantages in terms of its reliable effect and low cost; however, hCG products are available in the form of injectables that require a night-time hospital visit for administration just before the oocyte retrieval procedure on the next morning. On the other hand, GnRH-a can be self-administered at home without a night-time hospital visit and it is given as a nasal spray that does not cause pain. One of the disadvantages of GnRH-a is its cost; each oocyte retrieval imposes a high financial burden on patients. In addition, GnRH-a might be less effective for patients who are having intense symptoms of nasal discharge and congestion during the pollen allergy season (Table 1).[1]

Prior to the self-injection of hCG at home, the patients were given sufficient explanation by the clinic staff.[2] However, the administration of hCG is complex and can cause the risks of injection failures and ampule-related injuries due to its ampule-type drug formulation. The other disadvantages of conventional human urinary-hCG (u-hCG) include the contamination of various unknown proteins[3] and the potential batch-to-batch variation with regards to drug potency.[4] For these reasons, there were needs for commercially available prefilled recombinant hCG (r-hCG). In March, 2017, a long-awaited prefilled r-hCG in syringe was launched. In this article is reported the comparison of the efficacy and safety of self-injections of the prefilled r-hCG by syringe in ART treatment against the self-injections of conventional hCG and intranasal administration of GnRH-a.

2 | METHODS

This study's population consisted of 396 patients who underwent oocyte retrieval for ART at the clinic between January and April, 2017. Of these, 396 patients were classified into three groups, according to the method of the maturation trigger for oocyte retrieval. All the patients were enrolled consecutively in the present study at the Division of Reproductive Medicine, Sugiyama Clinic, Tokyo, Japan. This study was approved by the Institutional Review Board of the Sugiyama Clinic. A signed informed consent form was obtained from all the patients prior to entering the study.

For ovarian stimulation, either clomiphene citrate (Clomid®; Fuji Pharma Company, Ltd., Toyama, Japan) alone or Clomid® in combination with a recombinant follicle-stimulating hormone (Gonal-F®; Merck Serono Company, Ltd., Tokyo, Japan) was used.[5] In all these patients, the maturation trigger for oocyte retrieval was performed 35 hours before the planned oocyte retrieval and the patients were classified into one of the following three groups, according to the type of maturation trigger: (1) the u-hCG group that consisted of patients who had a self-injection of conventional u-hCG (hCG 5000 IU for i.m. injection; Mochida Pharmaceutical Company, Ltd., Tokyo, Japan); (2) the GnRH-a group that consisted of patients who received a nasal administration of GnRH-a (Buserecur®; Fuji Pharma Company, Ltd.) (300 μg/dose × 2 each time, given at 35 and 35.5 hours before oocyte retrieval); and (3) the r-hCG group that consisted of patients who had a self-injection of r-hCG (Ovidrel®; Merck Serono Company, Ltd.). The period for using either GnRH-a, u-hCG, or r-hCG as a maturation trigger was a criterion for classification of the three groups. The GnRH-a was used as a maturation trigger between January and February in 2017, u-hCG was used in March, 2017, and r-hCG was used in April, 2017. The oocyte retrieval was performed under transvaginal ultrasound guidance. For the method of insemination, conventional insemination or ICSI was selected, depending on the seminal findings. The embryo transfer was performed on day 3 or 5 after the oocyte retrieval. For the patients who underwent an embryo transfer, chlormadinone acetate (Lutoral®; Fuji Pharma Company, Ltd.) and hydroxyprogesterone caproate (Proge Depot 125 mg for i.m. injection; Mochida Pharmaceutical Company, Ltd.) were given for luteal support.[6]

TABLE 1 Characteristics of each formulation that was used for maturation triggering

Variable	hCG	GnRH-a
Route of administration	s.c./i.m. injection	Nasal
Night-time hospital visit	Required in principle[a]	Not required
Self-injection	Complicated procedure	—
Cost	~10US$	~110US$
Interproduct stability	Unstable	Stable
Other	—	Less effective in the presence of nasal discharge and congestion

GnRH-a, gonadotropin-releasing analog; hCG, human chorionic gonadotropin.
[a]Mean ± SD.

TABLE 2 Patient demographics of each group

Characteristic	u-hCG	r-hCG	GnRH-a
Patients (N)	127	110	159
Age (years)[a]	38.1 ± 4.4	38.1 ± 4.7	39.9 ± 3.9
Indication/unexplained infertility (N)	80	66	92
Male factors	38	37	58
Tubal factors	9	7	9
Ovarian stimulation/CC + FSH (N)	107	98	92
Antagonists	1	1	3
CC alone or natural cycle	19	11	64

CC, clomiphene citrate; FSH, follicle-stimulating hormone; GnRH-a, gonadotropin-releasing analog; r-hCG, recombinant human chorionic gonadotropin; u-hCG, urinary hCG.
[a]Mean ± SD.

2.1 | Methods of self-injection

At the current clinic, self-injection for the administration of gonadotropin and hCG was introduced in April, 2016 in order to reduce patients' burden related to hospital visits while receiving ART treatment. Prior to the initiation of self-injection, the patients were given explanations of self-injection first by using a brochure and a video and second by attending a self-injection explanatory meeting to see an actual self-injection demonstration and to hear the explanation.[2]

2.2 | Endpoints

Clinical pregnancy was defined as both a positive urine or blood hCG test and the presence of a gestational sac that was detected by transvaginal ultrasound. The authors evaluated the oocyte retrieval rate, the number of mature oocytes, degenerated oocytes, good-quality embryos, and the incidence of ovarian hyperstimulation syndrome (OHSS) in each group. The severity of OHSS was classified according to the Japan Society of Obstetrics and Gynecology's report.[7] Patients whose oocytes could not be collected were excluded from the evaluation. An unpaired *t*-test and a chi-square test were used for statistical evaluation. The statistical analyses regarding the pregnancy, implantation, and twin rates were performed by using a chi-square test. Statistical significance was set at $P < .05$.

3 | RESULTS

The patients' demographics in the three groups are shown in Table 2. There were 127, 110, and 159 patients in the u-hCG, r-hCG, and GnRH-a groups, respectively. The mean ages were 38.1 ± 4.4, 38.1 ± 4.7, and 39.9 ± 3.9 years, respectively, with no difference in the three groups. The indication for ART treatment did not differ between the three groups, while unexplained infertility was responsible for most of the indications in all three groups. For the method of ovarian stimulation, more than half of the patients in all groups

TABLE 3 Clinical parameters of ovarian stimulation in each group

Variable	u-hCG	r-hCG	GnRH-a
No. of oocytes collected (mean ± SD)	624 (4.9 ± 3.5)	497 (4.5 ± 3.3)	543 (3.4 ± 3.8)[a]
No. of mature oocytes (mean ± SD)	506 (4.0 ± 2.8)	447 (4.1 ± 2.9)	421 (2.6 ± 2.4)
No. of immature oocytes (mean ± SD)	75 (0.6 ± 0.7)	16 (0.1 ± 0.3)	68 (0.4 ± 0.7)
No. of degenerated oocytes (mean ± SD)	43 (.3 ± .5)	34 (.3 ± .6)	54 (.3 ± .6)
Mature oocyte retrieval rate (%)	81.1	89.9	77.5
Method of insemination (conventional insemination/ICSI) (N)	59/61	55/44	69/72
No insemination due to immature or deformed oocytes (N)	7	11	18
No. of fertilized oocytes (mean ± SD)	454 (3.6 ± 2.9)	397 (3.6 ± 2.0)	375 (2.4 ± 2.1)
Fertilization rate (%)	89.7	88.8	89.0
No. of cleavaged embryos (mean ± SD)	383 (3.0 ± 2.2)	341 (3.1 ± 1.9)	324 (2.0 ± 1.9)
Cleavage rate (%)	84.4	85.9	86.4

GnRH-a, gonadotropin-releasing analog; ICSI, intracytoplasmic sperm injection; r-hCG, recombinant human chorionic gonadotropin; SD, standard deviation; u-hCG, urinary hCG.
[a]Comparison with the u-hCG and r-hCG groups ($P < .05$).

TABLE 4 Clinical outcome of fresh embryo transfer in the three groups

Variable	u-hCG	r-hCG	GnRH-a
No. of fresh embryo transfer cycles	79.0	34.0	76.0
No. of embryos transferred (mean per cycle[a])	106.0 (1.3 ± 0.5)	68.0 (2.0 ± 0.5)	93.0 (1.2 ± 0.4)
hCG-positive (N)	22.0	14.0	17.0
hCG-positive rate (%)	27.8	41.1	22.3*
Clinical pregnancy (N)	20.0	13.0	12.0
Clinical pregnancy rate (%)	25.3	38.2	15.8
No. of multiple pregnancies	1.0	1.0	0.0
Incidence of multiple pregnancies (%)	5.0	7.6	0.0
Miscarriage (N)	5.0	1.0	3.0
Miscarriage rate (%)	25.0	7.7	25.0
Incidence of OHSS (%)	10.1	8.8	5.2

GnRH-a, gonadotropin-releasing analog; OHSS, ovarian hyperstimulation syndrome; r-hCG, recombinant human chorionic gonadotropin; SD, standard deviation; u-hCG, urinary hCG.
[a]Mean ± SD.
*$P < .05$ (compared with r-hCG)

received Clomid® in combination with Gonal-F®, while the proportion of patients who received Clomid® alone or elected to pursue a natural cycle was significantly higher in the GnRH-a group (40.3%), compared with those in the u-hCG group (15.0%) and the r-hCG group (10.0%, $P < .01$).

The clinical parameters of ovarian stimulation in the three groups are shown in Table 3. The mean number of oocytes collected (± standard deviation [SD]) was 4.9 ± 3.5, 4.5 ± 3.3, and 3.4 ± 3.8 in the u-hCG, r-hCG, and GnRH-a groups, respectively, and the number of oocytes that were collected in the GnRH-a group was significantly lower, compared with the u-hCG and r-hCG groups ($P < .05$, respectively). The mature oocyte retrieval rate was 81.1%, 89.9%, and 77.5% in the u-hCG, r-hCG, and GnRH-a groups, respectively, with no difference between the three groups. The fertilization rate and cleavage rates were 89.7% and 84.4%, respectively, in the u-hCG group, 88.8% and 85.9%, respectively, in the r-hCG group, and 89.0% and 86.4%, respectively, in the GnRH-a group and both the fertilization rate and cleavage rate showed no difference between the three groups.

The numbers of fresh embryo transfer cycles and transferred embryos (mean ± SD) were 79 and 1.3 ± .5 in the u-hCG, 34 and 2.0 ± .5 in the r-hCG, and 76 and 1.2 ± .4 in the GnRH-a groups, respectively. The proportions of patients with a positive hCG test were 27.8%, 41.1%, and 22.3% in the u-hCG, r-hCG, and GnRH-a groups, respectively, which is significantly lower for the GnRH-a group, compared with the r-hCG group. The clinical pregnancy rates did not significantly differ between the GnRH-a group (15.8%) and the u-hCG group (25.3%); however, it was significantly lower in the GnRH-a group, compared to the r-hCG group (38.2%) ($P < .05$). There was no significant difference between the u-hCG group and the r-hCG group. Also, there were no differences with the miscarriage rates and multiple pregnancy rates in the three groups (Table 4). No difference was observed in the incidence of moderate or more severe OHSS between the three groups.

4 | DISCUSSION

The ART outcomes were compared in all three types of oocyte maturation trigger while retrieving oocytes for ART treatment: self-injection of u-hCG, self-injection of r-hCG, and nasal administration of GnRH-a. To clarify whether or not the ART outcomes differed depending on the maturation trigger methods, several parameters were evaluated among the three groups. The mature oocyte retrieval rate was similar between the u-hCG group, the r-hCG group, and the GnRH-a group (81.1%, 89.9%, and 77.5%, respectively); thus, the self-injection of the newly launched r-hCG showed an equivalent outcome to the conventional methods. The fertilization rates and the cleavage rates were 89.7% and 84.4%, respectively, in the u-hCG group, 88.8% and 85.9%, respectively, in the r-hCG group, and 89.0% and 84.4%, respectively, in the GnRH-a group; this also indicates that the self-injection of r-hCG is equivalent to the conventional methods in both the fertilization and cleavage rates. The clinical pregnancy rate in the GnRH-a group was significantly lower than in the r-hCG group. There were two reasons why this difference occurred. One was the higher proportion of patients who used clomiphene citrate alone or a natural cycle in the GnRH-a group than the other two groups; consequently, the lower number of oocytes that was collected in the GnRH-a group. The other was the fact that the hCG showed a longer bio-potency than the GnRH-a, suggesting that the hCG that was used as a maturation trigger gave some effect on luteal support. Meanwhile, luteal support was started on day 3 after oocyte retrieval (day 5 after the maturation trigger) in all three groups in order to evaluate the

clinical pregnancy rate. In the GnRH-a group, the risk of OHSS was lower because the GnRH-a blood concentrations rapidly decreased after dosing; however, the clinical pregnancy rate after the fresh embryo transfer suggested that luteal support should be started immediately after oocyte retrieval in the GnRH-a group. During this study period, there were not many frozen-warmed embryo transfers. Until September, 2017, 21, 15, and 20 cycles were performed in the u-hCG, r-hCG, and GnRH-a groups, respectively. The clinical pregnancy rates in these three groups were 38.1%, 33.3%, and 35.0%, respectively.

The r-hCG that was used in this study is the first r-hCG in Japan that is indicated for "follicle maturation and luteinization in ART," whereby the raw material is free from human urine. As the r-hCG comes in a prefilled syringe formulation, it does not require reconstitution and thus can be easily administered. Regarding the clinical results of ART, there have been some reports comparing r-hCG with conventional u-hCG. In these reports, the GnRH-a long protocol was used for ovarian stimulation and the number of oocytes retrieved per patient and the clinical pregnancy rate were similar between the r-hCG and u-hCG.[8,9] In contrast, the incidence of adverse events of injection site reaction (eg, redness, swelling) was lower with r-hCG, compared with u-hCG.[10] This difference may be attributed to fewer contaminating proteins in the r-hCG. Similarly, u-hCG appeared to be associated with a higher incidence of local redness and swelling at the current study's clinic; patients' complaints with regards to these symptoms have been reduced drastically after switching to r-hCG completely.[11]

The authors already have conducted a survey for 120 patients who underwent ART treatment at the clinic in 2016 to see what the biggest burden was for them during their treatment and the results showed that 36% of all the patients responded that scheduling for hospital visits was the biggest burden, which was higher than financial issues and psychological stress.[3] Based on these results, the self-injection of gonadotropin and hCG was introduced in April, 2016 in order to reduce the burden that was associated with hospital visits. In order to train patients for self-injection, the patients were provided with brochures, a CD-R, and QR code for online training, which were all created by the clinic staff, and the patients were briefed with a self-injection demonstration and explanatory meetings on self-injection also were held. During the early phase of the introduction of self-injection, only 56% of the patients who received ovarian stimulation for ART selected self-injection; however, 6 months later, 75% of the patients decided to perform self-injection.[7] Two types of gonadotropin formulation (ampule and pen) were used for self-injection; however, there was only the one choice of an ampule for the hCG formulation at the time of the introduction of self-injection. The risks that were related to self-injection with an ampule included failing to maintain a sterile condition during the reconstitution and filling the drug solution from the ampule to the syringe: injuries when opening the ampule, a failure of accurate dosing due to a damaged ampule, and injection failure. In addition to the instructions mentioned above, the department provided a 24 hour telephone assistance service to the patients who chose self-injection. During the study period, the number of patients who made a mistake of self-injection in the u-hCG and r-hCG groups were one and zero, respectively, but this mistake was due to fracturing the ampule during preparation. In contrast, no patient made a mistake with the nasal spray. With hCG, unlike with the other gonadotropins, a single injection failure of hCG can lead to the termination of the treatment cycle. In order to avoid such risks, the authors had waited for a long time for the launch in March, 2017 of a prefilled syringe-type hCG in Japan and it has been implemented ever since it became commercially available. In ART treatment, hCG the drug (and its preparation) is very important and the data demonstrated that the efficacy of r-hCG was similar with that of conventional hCG. In addition, there were fewer side-effects observed in the r-hCG group, with no occurrence of damaging the syringe while preparing, unlike the u-hCG group. Currently, most of the patients administer hCG by self-injection, although the self-injection has not yet been approved. It is highly anticipated to have the early approval of r-hCG self-injection in order to reduce patients' burden by eliminating the necessity of hospital visits for injection.

DISCLOSURES

Conflict of interest: The authors declare no conflict of interest. *Human Rights Statement and Informed Consent*: This study was approved by the Institutional Review Board of Sugiyama Clinic, Tokyo, Japan. Written informed consent was obtained from each participant couple. *Animal studies:* This article does not contain any study with animal participants that have been performed by any of the authors.

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How to cite this article: 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. https://doi.org/10.1002/rmb2.12095