Original Article

A novel strategy of using corifollitropin alfa in the ultrashort gonadotropin-releasing hormone agonist (GnRHa) protocol in unselected patients: A patient-friendly alternative

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ABSTRACT

Objective: To compare the outcomes of in vitro fertilization (IVF) and fresh embryo transfer (ET) using corifollitropin alfa in ultrashort gonadotropin-releasing hormone agonist (GnRHa) protocol and GnRH antagonist protocol.
Materials and methods: A total of 245 unselected patients undergoing IVF/fresh ET were enrolled between January 1 and December 31, 2017, including 135 treated with ultrashort GnRHa protocol and 110 treated with antagonist protocol. The primary outcomes were number of total injections and outpatient department (OPD) visits before ovulation triggering. The secondary outcomes were the duration of stimulation, dosage of additional gonadotropin for ovarian hyperstimulation, rates of pregnancy, clinical pregnancy, live birth, ovarian response, and ovarian hyperstimulation syndrome (OHSS) rate.
Results: Patients treated with ultrashort GnRHa required less additional gonadotropin, fewer total injections, but had better ovarian responses, including more oocytes retrieved, more metaphase II oocytes, and more blastocysts than those treated with antagonist did. A premature LH surge occurred only in six patients treated with antagonist protocol. The rates of pregnancy (37.0% vs. 43.6%), clinical pregnancy (25.2% vs. 34.6%), and live birth (19.3% vs. 30.0%) did not differ significantly between the two groups. The OHSS rate was similar in the two groups.
Conclusion: In unselected patients using corifollitropin alfa, the ultrashort GnRHa protocol needed lower dose of additional gonadotropin and fewer injections but produced similar pregnancy outcomes than antagonist protocol did, suggesting that the ultrashort GnRHa protocol could be an alternative.

Introduction

Controlled ovarian hyperstimulation (COH) recruits several fertilizable oocytes and produces as many good-quality embryos as possible without increasing the risk of adverse effects, such as ovarian hyperstimulation syndrome (OHSS) to achieve success in assisted reproductive technology (ART) [1,2]. One of the fundamental aspects of COH is preventing a premature luteinizing hormone (LH) surge that might disturb the normal development of follicles [3,2]. Gonadotropin-releasing hormone (GnRH) agonists and antagonists are two common medications used to block the premature LH surge [3].

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Gonadotropin-releasing hormone agonist (GnRHa) has been used to desensitize the pituitary gland for decades. It is thought to prevent the premature LH surge before ovulation induction and to decrease the cycle cancellation rate [4,5]. Long-term administration of GnRHa from the previous mid-luteal phase (i.e., the long protocol) may cause excessive suppression of the pituitary gland and compromise the ovarian response to COH [6]. The long protocol may also extend the stimulation duration and require more doses of exogeneous gonadotropins for an adequate ovarian response [7]. The use of GnRHa concomitantly with exogenous gonadotropins in the early follicular phase (i.e., the short protocol or GnRHa flare-up protocol) was proposed in 1988 [7]. The short protocol avoids the excessive ovarian suppression, and causes an additional stimulating flare-up effect in the pituitary gland, which in turn causes immediate endogenous gonadotropin release. This release of gonadotropin may aid follicular recruitment and, theoretically, may reduce the requirement for exogenous gonadotropins [8,9]. In the short protocol, GnRHa is used continuously until induction of ovulation, which has a suppressive effect on the endogenous LH surge [10]. An ultrashort GnRHa protocol, comprising GnRHa for only 3 consecutive days in the early follicular phase followed by exogenous gonadotropin administration could avoid excessive ovarian suppression further [7,11].

GnRH antagonists have been used in COH since the 1990s [12]. These antagonists rapidly inhibit endogenous gonadotropin release within hours, which prevents the premature LH surge, decreases cycle cancellation rate, lowers the incidence of OHSS, and is associated with an acceptable live birth rate of 25–33% [13]. The antagonist protocols have gradually replaced the GnRHa-downregulation protocol because of the lower dose of gonadotropins required for COH and the shorter duration of stimulation, without compromising the pregnancy rate [14].

Exogenous gonadotropins have been used to recruit multiple follicles for *in vitro* fertilization (IVF) since the 1970s [15]. Because of the short elimination half-life and rapid metabolic clearance, daily injection of gonadotropins is needed to maintain a stable serum level. Using recombinant DNA technologies, a long-acting follicle-stimulating hormone (FSH) molecule was developed, i.e., corifollitropin alfa [16]. Because of the extended duration of the FSH serum level above the activity threshold, a single injection of corifollitropin alfa can support the development of multiple follicles for one week [15,17]. Reducing the number of gonadotropin injections may alleviate the burden of IVF and increase the compliance of patients.

To our knowledge, no study has investigated the use of corifollitropin alfa in the ultrashort GnRHa protocol. The present study aimed to compare the outcomes of IVF and fresh embryo transfer (ET) in unselected infertile patients undergoing COH with corifollitropin alfa between the ultrashort and antagonist protocols.

Material and methods

Study design

All patients undergoing COH cycles in our infertility center in Taipei Medical University Hospital between January 1 and December 31, 2017 were assessed for eligibility. Patients receiving corifollitropin alfa in the ultrashort or antagonist protocol for IVF and fresh ET were included in our analysis. The choice of protocol was based on the physician's preference. The requirements for enrollment in these two protocols included a cycle day 2 or 3 serum FSH concentration less than 10 mIU/mL, a serum E_2 concentration less than 80 pg/mL, and no evidence of follicular development or ovarian cyst larger than 3 cm existence or obvious corpus luteum cysts on transvaginal ultrasonography. Women with polycystic ovary syndrome (PCOS) were excluded according to the instruction

of corifollitropin alfa. The study was approved by the ethics committee of Taipei Medical University Hospital (Institutional Review Board Number: N201711084), and as this was a retrospective study, the need for informed consent was waived.

The primary outcomes were number of total injections, and number of OPD visits before ovulation trigger. The secondary outcome measures were the duration of stimulation, dosage of additional gonadotropins, the pregnancy rate, clinical pregnancy rate, live birth rate, cumulative pregnancy rate, ovarian response to COH and OHSS rate.

Ovarian stimulation protocols

In the ultrashort GnRHa protocol, 1 mg of leuprolide acetate (Lupro® 14 mg/2.8 mL/vial; Nang Kuang) was given subcutaneously on cycle days 2, 3, and 4. A single injection of corifollitropin alfa (Elonva®; MSD) was used on day 3, and the dosage was determined according to the medication instruction. Next, 6–7 days after corifollitropin alfa injection, follicle development was monitored by transvaginal sonography, and the serum hormone levels of estradiol (E_2), progesterone (P_4), and LH were measured. Follitropin alfa (Gonal-f®; Merck Sereno) and/or hMG (Menopur®; Ferring, or Merional®; IBSA) were administered according to the ovarian response and the dosage was adjusted (Fig. 1). Follicle development and serum hormone levels were monitored depending on the patient's condition.

In the antagonist protocol, corifollitropin alfa (Elonva®; MSD) was injected on cycle day 2. Next, 6–7 days later, follicle development and serum hormone levels were measured. Follitropin alfa (Gonal-f®; Merck Sereno) and/or hMG (Menopur®; Ferring, or Merional®; IBSA) were administered according to the ovarian response and the dosage was adjusted. Once the leading follicle reached 14 mm in diameter and/or serum E_2 level was >500 pg/mL [12], 0.125 mg per day of cetrorelix (Cetrotide®; Merck Sereno) was administered subcutaneously and continued until the day of ovulation triggering.

When at least three leading follicles reached >17 mm in diameter, hCG 1500–6500 IU (Ovidrel®; Merck Sereno) with or without 1 mg of leuprolide acetate (Lupro® 14 mg/2.8 mL/vial; Nang Kuang) were administered subcutaneously to trigger ovulation for patients undergoing both ultrashort GnRHa protocol and antagonist protocol, depending on the risk of OHSS and the physician's preference. The efficacy of ovulation trigger by GnRHa in the ultrashort GnRHa protocol was demonstrated by Orvieto [18].

Oocyte retrieval and ET

Transvaginal oocyte retrieval was performed 34–36 h after the hCG injection, followed by *in vitro* fertilization, or intracytoplasmic sperm injection (ICSI) for couples with male factor infertility, fertilization failure in a prior *in vitro* fertilization, unexplained infertility or low oocyte yield, et al. [19,20]. Fresh ET was performed 3 or 5 days after retrieval. Surplus embryos were vitrified. Vaginal micronized progesterone gel (Crinone® 8% 90 mg/applicator; Merck Serono) was given once a day since the ET day. Hydroxyprogesterone caproate 250 mg (Progeston Depot-S® 125 mg/amp; Fuji Pharma) was used intramuscularly and weekly, according to the physician's preference. Luteal support continued to 8–10 weeks of gestation or until failure of pregnancy was confirmed.

Outcomes measurement

The demographic parameters included age, body mass index (BMI), serum anti-mullerian hormone (AMH) level, primary or secondary infertility, and the indications for ART.
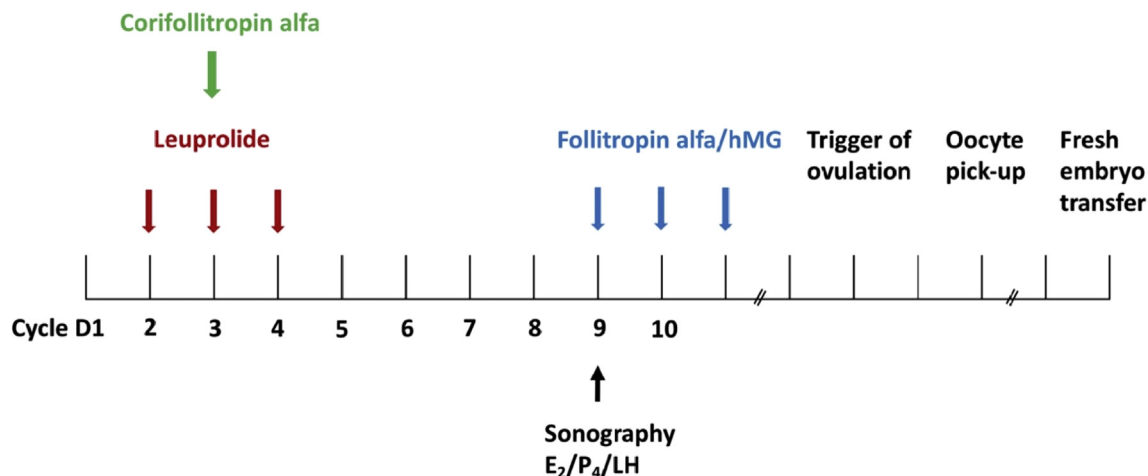
Fig. 1. The ultrashort GnRHa protocol with corifollitropin alfa. Note: D = day; E_2 = estradiol; hMG = human menopausal gonadotropin; LH = luteinizing hormone; P_4 = progesterone.

The response of ovarian stimulation was recorded along with stimulation duration in days, total dose of additional gonadotropins, number of total injections, number of OPD visits after the first visit, serum hormone profiles before ovulation triggering (including E_2, P_4, and LH), incidence of premature LH surge (>10 IU/L or elevated basal level more than twice that before triggering), endometrial thickness before triggering, number of oocytes retrieved, number and percentage of mature oocytes, fertilization rate, percentage of cleavage-stage embryos, top-quality day 3 embryo rate, blastocyst formation rate, number of frozen embryos, and incidence of OHSS. A top-quality day 3 embryo was defined as ≥8 cells of regular size, <10% fragmentation, and no multinucleation [21]. OHSS was diagnosed and managed according to Pfeifer et al. [22].

The pregnancy outcomes were recorded as pregnancy rate, clinical pregnancy rate, live birth rate and cumulative pregnancy rate. Urine and serum β-hCG levels were measured 14 days after day 3 embryo transfer, or 12 days after blastocyst transfer. If the serum β-hCG level was above 30 IU/L, then pregnancy was confirmed. Biochemical pregnancy was defined as a transient elevation of β-hCG without ultrasound evidence of pregnancy. Clinical pregnancy was the presence of gestational sac(s) with fetal heartbeat(s) on ultrasound scan at 6 or 7 weeks of gestation. Live birth was defined as delivery of at least one live newborn after 24 weeks of gestation. The cumulative pregnancy took account of all pregnancies achieved in the fresh ET or all the frozen ET resulting from one round of ovarian stimulation cycle.

Statistical analysis

The data are expressed as mean ± standard deviation, frequencies (number of cases), or percentages when appropriate. Numerical variables were compared between two groups using Student's *t* test for independent samples. Chi-square (χ^2) analysis was used to compare categorical data. All statistical calculations were performed using the Statistical Package for Social Sciences (IBM® SPSS® Statistics) version 24 for Mac. A *P* value < 0.05 was considered to be significant.

Results

From January 1 to December 31, 2017, IVF and fresh ET were applied for 135 patients using ultrashort protocol with corifollitropin alfa and 110 patients in the antagonist protocol with corifollitropin alfa. The patients' demographics are listed in Table 1.

The mean age, BMI, AMH and ratios of primary and secondary infertility were similar in both groups. The tubal factor was the most common single indication for ART in both groups.

Comparisons of primary and secondary outcomes between two stimulation groups are presented in Table 2 and Table 3. Although the total stimulation duration was longer and the number of OPD visits before ovulation triggering was more in patients treated with ultrashort GnRHa protocol than those treated with antagonist protocol, the total dosage of additional gonadotropin and the total number of injections before ovulation triggering were lower in the former.

The serum LH level before ovulation triggering was lower in patients with ultrashort GnRHa protocol than that with antagonist protocol (1.12 ± 0.77 vs. 4.12 ± 6.81 mIU/mL, *P* < 0.001). For premature LH surge, none occurred in ultrashort GnRHa protocol but 6 patients did in antagonist protocol. For primary outcome evaluation, patients treated with ultrashort GnRHa protocol had a better ovarian response than those treated with antagonist protocol, including higher maximal E_2 level, higher number of oocytes retrieved, higher number of metaphase II (MII) oocytes, higher number of fertilized oocytes, and higher number of blastocysts than those treated with antagonist protocol did. With corifollitropin alfa, the ultrashort protocol seemed to produce more oocytes and embryos than the antagonist protocol.

No significant differences were observed between the two groups in P_4 level before triggering, maximal endometrial thickness, MII oocyte rate, fertilization rate, cleavage-embryo rate, top-quality D3 embryo rate, and total number of frozen embryos. The pregnancy rate, clinical pregnancy rate, and live birth rate were also similar between the two groups. Accumulative pregnancy (both fresh and frozen ET) was analyzed by 127 patients treated with ultrashort GnRHa protocol and 109 treated with antagonist protocol, and the results showed that 60 and 56 had become pregnant, respectively, contributing to the similar cumulative pregnancy rates per oocyte pick-up between the two groups (47.24% vs. 51.38%, *P* = 0.527). Although there were two patients treated with ultrashort GnRHa protocol who developed mild OHSS, which did not reach the statistically significant difference when comparing with patients treated with antagonist protocol.

Discussion

To our knowledge, this is the first observational study to compare the use of corifollitropin alfa in the ultrashort GnRHa protocol with the antagonist protocol in general patients

Table 1
Patient demographics.

	Ultrashort (n = 135)	Antagonist (n = 110)	*P* value
Age (y)	37.04 ± 4.28 (26–47)	36.56 ± 4.26 (27–46)	0.382
BMI (kg/m^2)	21.69 ± 2.95 (16.8–30.7)	22.24 ± 3.55 (16.4–34.9)	0.189
AMH (ng/mL)	2.58 ± 1.92 (0.31–9.20)	2.19 ± 2.21 (0.07–14.17)	0.142
Primary: secondary infertility	61:74	55:55	
Indications for IVF/ICSI			
Tubal	25 (18.52%)	16 (14.55%)	
Male	21 (15.56%)	10 (9.09%)	
Endometriosis	3 (2.22%)	14 (12.73%)	
Aged	13 (9.63%)	5 (4.55%)	
DOR	8 (5.93%)	13 (11.82%)	
Uterine	5 (3.70%)	0	
Vaginismus	1 (0.74%)	0	
Combined	34 (25.19%)	43 (39.09%)	
Unexplained	25 (18.52%)	9 (8.18%)	

Note: Variables are presented as mean ± standard deviation, frequencies (number of cases), or percentages. *P* value < 0.05 was considered to be significant. AMH = anti-mullerian hormone; BMI = body mass index; DOR = diminished ovarian reserve; ICSI = intracytoplasmic sperm injection; IVF = *in vitro* fertilization.

Table 2
IVF outcomes in the two groups.

	Ultrashort (n = 135)	Antagonist (n = 110)	*P*-value
Stimulation days	10.30 ± 1.52 (8–14)	8.88 ± 1.30 (4–13)	<0.001***
No. of visits before trigger	2.04 ± 0.74 (1–5)	1.70 ± 0.64 (1–3)	<0.001***
No. of shots before trigger	6.63 ± 1.88 (4–12)	8.62 ± 2.81 (1–14)	<0.001***
Additional FSH dosage (IU)	637.78 ± 537.63 (0–2250)	802.95 ± 435.97 (0–2100)	0.010*
LH (mIU/ml) before trigger	1.12 ± 0.77 (0.07–3.59)	4.12 ± 6.81 (0.33–57.83)	<0.001***
Premature LH surge rate	0% (0)	5.45% (6)	0.006**
Maximal E$_2$ level (pg/ml)	2333.87 ± 1441.06 (211.3–7170.0)	1903.43 ± 1028.72 (239.5–5258.9)	0.009**
P$_4$ before trigger (ng/ml)	0.82 ± 0.48 (0.11–2.98)	0.75 ± 0.35 (0.21–1.94)	0.236
EM thickness (mm)	10.68 ± 2.38 (6.00–19.00)	10.59 ± 1.99 (6.80–18.00)	0.759
No. of oocytes retrieved	12.52 ± 8.12 (1–42)	9.40 ± 7.03 (1–33)	0.002**
No. of MII oocytes	8.93 ± 6.02 (1–35)	6.02 ± 5.58 (0–29)	<0.001***
MII rate (%)	73.38 ± 20.45 (13–100%)	68.40 ± 15.01 (0–100%)	0.642

Note: Variables are presented as mean ± standard deviation, frequencies (number of cases), or percentages. *P* value < 0.05 was considered to be significant. E$_2$ = estradiol; EM = endometrial; FSH = follicle-stimulating hormone; LH = luteinizing hormone; MII = metaphase II.
* p < 0.05, ** p < 0.01, *** p < 0.001.

Table 3
Embryo and pregnancy outcomes in the two groups.

	Ultrashort (n = 135)	Antagonist (n = 110)	*P*-value
Fertilization rate (%)	71.99 ± 19.62 (17.00–100%)	71.41 ± 20.69 (10.00–100%)	0.821
Cleavage rate (%)	94.81 ± 10.90 (40–100%)	95.82 ± 11.80 (40–100%)	0.488
Top quality embryo rate (%)	53.20 ± 26.60 (0–100%)	50.53 ± 31.26 (0–100%)	0.470
No. of blastocyst	2.89 ± 3.46 (0–15)	1.94 ± 3.44 (0–20)	0.033*
Blastocyst rate (%)	33.81 ± 31.96 (0–100%)	21.05 ± 31.26 (0–100%)	0.002**
No. of surplus frozen embryos	2.36 ± 3.28 (0–18)	1.92 ± 3.22 (0–19)	0.283
No. of patients having frozen embryos	54.81% (74)	44.55% (49)	0.110
No. of embryo transferred	2.39 ± 0.89 (1–4)	2.41 ± 0.92 (1–4)	0.869
Pregnancy rate (%)	37.04% (50)	43.64% (48)	0.294
Clinical pregnancy (%)	25.19% (34)	34.55% (38)	0.110
Live birth rate (%)	19.26% (26)	30.00% (33)	0.051
Cumulative pregnancy rate (%)	47.24% (60/127)	51.38% (56/109)	0.527
OHSS rate (%)	1.48% (2)	0% (0)	0.200

Note: Variables are presented as mean ± standard deviation, frequencies (number of cases), or percentages. *P* value < 0.05 was considered to be significant. OHSS = ovarian hyperstimulation syndrome.
* p < 0.05, ** p < 0.01, *** p < 0.001.

undergoing IVF/ICSI and fresh ET. We included all unselected patients who received one of these two protocols for COH during the study period, and we compared the IVF and pregnancy outcomes. We found that the outcomes of ovarian response were better in the ultrashort protocol with corifollitropin alfa than in the antagonist protocol, as shown by the maximal E$_2$ level, number of oocytes retrieved, number of MII oocytes, and number and rate of blastocysts. Except for the corifollitropin alfa used in both protocols, the average dose of additional gonadotropins and number of total injections were lower in the ultrashort than in the antagonist protocol. Nevertheless, no significant differences were observed in the MII oocyte rate, fertilization rate, cleavage rate, top-quality D3 embryo rate, and number of frozen embryos between the two protocols. The pregnancy rate, clinical pregnancy rate, cumulative pregnancy rate, and live birth rate were also similar in both groups. The use of corifollitropin alfa in the ultrashort GnRHa protocol resulted in similar pregnancy outcomes, but with a lower additional gonadotropin dosage and fewer total injections; these observations suggest that it is an effective and patient-friendly protocol.

High LH levels may cause luteinization of the preovulatory follicles and premature terminal growth changes in the granulosa cells and oocytes [11]. This could affect the quality of oocytes, and lead to failure of implantation, which results in a lower pregnancy rate and a higher abortion rate compared with lower LH levels [23]. GnRHa was introduced into COH protocols in the late 1980s, with the intention of preventing the premature LH surge and ovulation [24]. Macnamee et al. reported that daily injection of buserelin at a dose of 500 μg/day for at least 10 days before COH attenuated the high LH level and increased the pregnancy rate [25]. However, in that study, use of GnRHa for a long period desensitized the pituitary gland, and a longer duration of stimulation and more doses of gonadotropins were required to achieve adequate follicular development. Howles et al. used buserelin at 500 μg/day on cycle days 1, 2, and 3, followed by exogenous gonadotropin stimulation. The plasma and urinary LH levels in the late follicular phase were lower than those in the previous CC/hMG cycles, and the pregnancy rate was 42.86% [7]. Macnamee et al. proposed the first prospective trial of the ultrashort-term use of GnRHa in COH in 1989, using buserelin at 500 μg/day on cycle days 2, 3, and 4, followed by hMG stimulation [11]. The ultrashort GnRHa protocol resulted in a lower LH level, more oocytes retrieved, and a higher pregnancy rate compared with CC/hMG cycles. No premature LH surge was noted in the ultrashort GnRHa group, but it occurred in 19% of patients in the CC/hMG group [11].

Some authors have used the GnRH antagonist in their ultrashort GnRHa protocol to prevent premature LH surge; i.e., the ultrashort GnRHa/GnRH antagonist protocol [5,26–28]. However, they did not mention the incidence of premature LH surge during the IVF cycle and the efficacy of the use of the GnRH antagonist in the ultrashort GnRHa/GnRH antagonist protocol. In our study, no premature LH surge occurred in the ultrashort protocol with corifollitropin alfa, which suggests that the antagonist may not be required in this protocol.

The ultrashort use of GnRHa in the early follicular phase could induce immediate endogenous gonadotropin secretion—the "flare-up effect"—which facilitates follicular recruitment. The FSH and LH levels would be maximal on the second day of GnRHa administration and would then be suppressed after day 3 [29–31]. In our study, corifollitropin alfa was injected one day after GnRHa administration; in other words, on the day the maximal FSH and LH levels occurred. Because of the slow absorption of corifollitropin alfa, the peak FSH levels occur within 2 days after injection corifollitropin alfa [15]. Therefore, in our ultrashort protocol using corifollitropin alfa, the serum FSH levels were persistently high, and the long duration of FSH activity above the threshold may have contributed to the recruitment of more follicles. This may explain why the total dose of additional gonadotropin and number of gonadotropin injections were lower in the ultrashort protocol than in the antagonist protocol (Table 2).

Marcus et al. compared the IVF outcomes between the ultrashort protocol and the long protocol, and found that more patients undergoing the long protocol had supernumerary embryos cryopreserved and a higher delivery rate. They proposed that the flare-up effect was detrimental to the quality of oocytes and embryos, so they recommended the use of the long protocol for all IVF patients [32]. Surrey et al. described a rescue effect of the corpus luteum from a previous cycle caused by the follicular phase administration of GnRHa and observed that elevated serum LH, progesterone, and androgen levels were detrimental to the IVF outcome [33]. Nevertheless, in a prospective paired observational study, high progesterone level seemed to have no negative consequences for IVF [34]. Besides, progestin-primed ovarian stimulation (PPOS) was proposed in recent years based on the observation that a high progesterone level during COH does not compromise the quality of oocytes and IVF outcomes [35,36]. In the current study, the pregnancy outcomes were similar in patients undergoing ultrashort protocol and antagonist protocol, showing the comparable oocyte quality and endometrium receptivity in these two protocols. Besides, COH is started only after we exclude the existence of ovarian cysts larger than 3 cm or obvious corpus luteum cysts using transvaginal sonography for routine baseline screening. Therefore, no elevation of serum progesterone was found during COH with the ultrashort protocol using corifollitropin alfa.

The application of the GnRH antagonist protocol offers some benefits to IVF outcomes, including shorter stimulation duration, lower required gonadotropin dose, and lower cycle cancellation rate, despite conflicting results for pregnancy outcomes [37,38]. Without the over-suppression effects on the ovary, the GnRH antagonist protocol is thought to be a more cost-effective protocol for infertile patients. Nevertheless, in current study, we used the long-acting corifollitropin alfa to substitute the daily gonadotropin injections in the ultrashort and antagonist protocols, and we found that lower dosages of additional gonadotropin and fewer total injections were required in the ultrashort protocol. At the same time, the ovarian responses to COH were significantly higher in the ultrashort than in the antagonist protocol (Table 2). Some patients in the ultrashort group came to OPD visits for follow-up of sonography and serum hormone levels without receiving additional gonadotropin; i.e., the "coasting strategy." Because there was no premature LH surge in the ultrashort group and the follicular development was acceptable, the decreased the frequency of OPD visits and shortened stimulation duration should be considered for further patient convenience.

The limitations of our study are its retrospective observation design and limited number of unselected patients. Although the pregnancy outcome was similar in both groups, there was a trend of higher pregnancy rate, clinical pregnancy rate, cumulative pregnancy rate and live birth rate in patients undergoing antagonist protocol. The etiology of this finding should be further analyzed, such as the effect of cleavage stage or blastocyst transferred. Additional prospective randomized control studies with larger sample sizes are still needed to evaluate further the feasibility of the ultrashort protocol with corifollitropin alfa. The subgroups of patients who benefit from this protocol should also be investigated.

Conclusions

In conclusion, our results suggest that the ultrashort GnRHa protocol with corifollitropin alfa is as efficacious as the antagonist protocol with corifollitropin alfa in unselected infertile patients undergoing IVF and fresh ET. This protocol may offer an alternative to the antagonist protocol with corifollitropin alfa for infertile patients seeking to reduce the dose and number of injections of gonadotropins without compromising the outcome of IVF and fresh ET.

Conflicts of interest

There is no conflict of interest.

Acknowledgments

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