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Early gonadotropin-releasing hormone antagonist start improves follicular synchronization and pregnancy outcome as compared to the conventional antagonist protocol

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Objective: To assess whether an early GnRH antagonist start leads to better follicular synchronization and an improved clinical pregnancy rate (CPR).
Methods: A retrospective cohort study. A total of 218 infertile women who underwent IVF between January 2011 and February 2013. The initial cohort (Cohort I) that underwent IVF between January 2011 and March 2012 included a total of 68 attempted IVF cycles. Thirty-four cycles were treated with the conventional GnRH antagonist protocol, and 34 cycles with an early GnRH antagonist start protocol. The second cohort (Cohort II) that underwent IVF between June 2012 and February 2013 included a total of 150 embryo-transfer (ET) cycles. Forty-three cycles were treated with the conventional GnRH antagonist protocol, 34 cycles with the modified early GnRH antagonist start protocol using highly purified human menopause gonadotropin and an addition of GnRH agonist to the luteal phase support, and 73 cycles with the GnRH agonist long protocol.
Results: The analysis of Cohort I showed that the number of mature oocytes retrieved was significantly higher in the early GnRH antagonist start cycles than in the conventional antagonist cycles (11.9 vs. 8.2, $p=0.04$). The analysis of Cohort II revealed higher but non-significant CPR/ET in the modified early GnRH antagonist start cycles (41.2%) than in the conventional antagonist cycles (30.2%), which was comparable to that of the GnRH agonist long protocol cycles (39.7%).
Conclusion: The modified early antagonist start protocol may improve the mature oocyte yield, possibly via enhanced follicular synchronization, while resulting in superior CPR as compared to the conventional antagonist protocol, which needs to be studied further in prospective randomized controlled trials.

Keywords: Follicular synchronization; GnRH antagonist; LH

Introduction

The introduction of gonadotropin-releasing hormone (GnRH) antagonists in assisted reproductive technology (ART) has provided a promising prospect of a more patient-friendly protocol. As antagonist-mediated suppression is immediate [1], it is possible to administer an antagonist at the time of the expected premature luteinization with a LH surge. The GnRH antagonist is started either on day 6 of stimulation or when the leading follicle size reaches 12–14 mm during controlled ovarian stimulation (COS) [2]. GnRH antagonist cycles

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also have the benefit of a shorter duration of COS, lower gonadotropin requirements, and lower incidence of ovarian hyperstimulation syndrome (OHSS) than the GnRH agonist cycles. However, systematic review results have failed to show an advantage of the antagonist use in terms of pregnancy rates when compared with the GnRH agonist long protocol [2,3].

The perceived lower clinical pregnancy rates (CPRs) in the antagonist cycles than in the agonist cycles are still considered problematic. A physiological increase in the FSH level during the luteal-follicular transition phase (interphase), in the GnRH antagonist cycles may result in heterogeneous follicular development, leading to slightly lower mature oocyte yield [4,5]. The presence of such asynchronized follicular growth may result in decreased mature oocyte yield. Consequently, fewer embryos may develop, and hence, the selection of good-quality embryos for transfer may be limited.

Several strategies have been suggested in GnRH antagonist cycles to improve follicular synchronization: oral contraception pretreatment [6-8], luteal E_2 pretreatment [9], and premenstrual administration of GnRH antagonist [10,11]. However, the premenstrual strategies may not be patient-friendly, since the patients have to wait for the next menstrual cycle to start their controlled ovarian stimulation (COS) and the total treatment duration for a given COS may thus be increased substantially [6,7,9]. Patients may prefer to undergo IVF during their current menstrual cycle.

We investigated whether an early GnRH antagonist start results in a better follicular synchronization, in turn leading to increased mature oocyte yield. The exact timing of the interphase increase in the FSH level is difficult to estimate due to the inherent variability of the FSH increase, which can occur before or at the beginning of menses or during the early follicular phase [12-14]. Therefore, it is believed that the interphase peak FSH increase can be inhibited by early GnRH antagonist administration initiated from the beginning of the menstrual cycle; such an early suppression of endogenous FSH may be advantageous for achieving follicular synchronization.

We evaluated this theme retrospectively in two consecutive cohorts. In the first cohort of patients, we compared the IVF outcomes between conventional and early GnRH antagonist start protocols to evaluate follicular synchronization. After assessing the results of the first cohort, we tried to optimize the early GnRH antagonist start protocol using gonadotropins with LH activity for COS and GnRH agonist addition to the luteal phase support (LPS) in the second cohort.

Methods

1. Patients

A total of 218 infertile women undergoing IVF between January 2011 and February 2013, divided into the abovementioned two patient cohorts, were included in the present retrospective analysis. The inclusion criteria were female age <38 years, body mass index (BMI) <25 kg/m^2, regular menstrual cycles without polycystic ovary syndrome and endometriosis, and first IVF cycle with the assigned protocol.

The initial cohort (Cohort I) of patients who underwent IVF between January 2011 and March 2012 included a total of 68 attempted IVF cycles. Thirty-four cycles were treated with the conventional GnRH antagonist multi-dose flexible protocol and 34 cycles with the early GnRH antagonist start protocol. We assessed the effect of the early initiation of GnRH antagonist administration on follicular synchronization. The primary outcome measure of the first cohort was the number of mature oocytes retrieved.

After analyzing the initial cohort's results, profound LH suppression was checked on stimulation day 5 with a mean of 0.9 IU/L. The initial cohort failed to show better pregnancy rates in early GnRH antagonist start cycles albeit higher mature oocyte yield compared to conventional antagonist cycles. Therefore, the early GnRH antagonist start protocol was modified using gonadotropins with LH activity from stimulation day 5 during COS and GnRH agonist addition to the LPS.

The second cohort (Cohort II) of patients who underwent IVF between June 2012 and February 2013 included a total of 150 ET cycles. Forty-three cycles were treated with the conventional antagonist protocol, 34 cycles with the modified early GnRH antagonist start protocol, and 73 cycles with the GnRH agonist long protocol. In the second cohort, the primary outcome measure was CPR/ET.

2. Conventional GnRH antagonist multi-dose flexible protocol

COS was initiated from the third day of menstruation using recombinant FSH (rFSH). GnRH antagonist (0.25 mg/day; Cetrotide, Merck Serono SA, Geneva, Switzerland) was administered when the leading follicle diameter was 12 mm. The initial daily dose of rFSH was either 225 or 300 IU depending on age, BMI, and anti-Müllerian hormone (AMH) levels, and the dose was then adjusted according to the ovarian response.

3. Early GnRH antagonist start protocol

Thirty four cycles of Cohort I underwent the early antagonist start protocol. GnRH antagonist was initiated from the second day of menses, and ovarian stimulation using rFSH (Gonal-F, Merck Serono SA) was started from the third day of menstruation.

Final oocyte maturation was triggered with a one-time dose of 250 μg of recombinant human chorionic gonadotropin (rhCG, Ovidrel, Merck Serono SA) when the average leading follicle diameter was equal to or more than 18 mm. Ultrasound-guided oocyte retrieval was performed 36 hours following rhCG administration, and embryos were transferred at the cleavage stage on day 3 of development. LPS was provided by a 50-mg intramuscular (IM) injection of proges-

terone (P4, Progesterone in oil, Watson Pharmaceuticals Inc., Parsippany, NJ, USA) daily, starting on the day of oocyte retrieval, and LPS was continued for another 6 to 8 weeks when a pregnancy was achieved. The primary outcome measure was the number of mature oocytes retrieved.

4. Modified early GnRH antagonist start protocol

Thirty-four cycles of the second cohort underwent the modified early GnRH antagonist start protocol. Cetrotide (0.25 mg) daily was initiated from the second day of menses, and COS using rFSH was initiated the day after commencing cetrotide. The gonadotropin formula was then switched from rFSH to highly purified human menopause gonadotropin (HP-HMG, Menopur, Ferring, Malmo, Sweden) starting from stimulation day 5 to offset the presumed profound endogenous LH suppression induced by early GnRH antagonist administration. For final oocyte maturation, 250 μg of rhCG was administered when the leading follicle size was equal to or more than 18 mm. The LPS was provided by daily P4 IM injection (progesterone in oil, Watson Pharmaceuticals Inc., Parsippany, NJ, USA) starting on the day of oocyte retrieval. GnRH agonist, triptorelin (0.1 mg, Decapeptyl, Ferring) was also added for luteal support as a single dose administered three days after the embryo transfer (Figure 1).

5. Statistical analysis

The data are expressed as mean ± SD. For statistical comparisons, clinical outcomes were analyzed using the chi-squared test and Student's *t*-test. Comparisons among the three groups were performed with one-way analysis of variance by using Tukey's B test for post-hoc comparisons. A value of $p < 0.05$ was considered statistically significant.

Results

1. Cohort I: effect of early initiation of GnRH antagonist on follicular synchronization

In the first cohort of patients, there were no differences between the treatment groups in terms of the means of female age (34.1 years vs. 34.2 years), BMI (21.4 kg/m^2 vs. 22.3 kg/m^2), and serum AMH levels (3.6 ng/mL vs.3.2 ng/mL) between the conventional and the early GnRH antagonist start cycles. The means of the E_2 level on the day of hCG administration (2,533.6 pg/mL vs. 3,432.9 pg/mL) and of the total number of retrieved oocytes (11.4 vs. 14.4) tended to be higher in the early antagonist start cycles; however, none of these differences showed any statistical significance. The mean number of mature oocytes was significantly higher in the early antagonist start protocol than in the conventional antagonist cycles (8.2 vs. 11.9, $p = 0.04$), and the ratio of the number of mature oocytes to the total number of oocytes was significantly higher in the early antagonist start cycles (71.9% vs. 82.6%). The CPR showed no statistically significant differences between the two groups (26.5% vs. 23.5%, non specific) (Table 1). In early GnRH antagonist start cycles, the mean LH level on stimulation day 5 was 0.92 ± 0.47 IU/L. The LH levels were not checked in the conventional antagonist cycles.

2. Cohort II: CPR of modified early GnRH antagonist start protocol

There were no differences in the patients' mean age, previous IVF cycle numbers, and serum AMH levels between the two groups. The IVF outcomes between the conventional and the modified early GnRH antagonist start cycles showed a similar trend to that of the

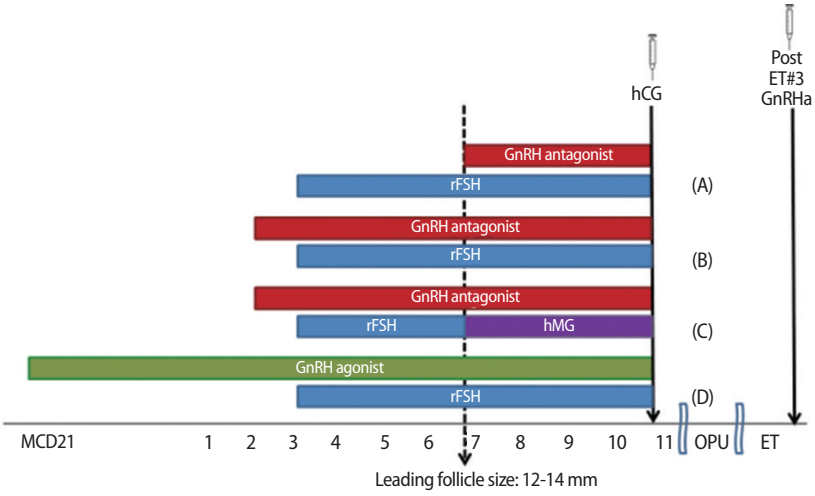

Figure 1. Schematic representation of each IVF protocol. (A) Conventional GnRH antagonist multi-dose flexible protocol. (B) Early GnRH antagonist start protocol with rFSH. (C) Modified early GnRH antagonist protocol using HP-HMG and GnRH agonist addition for luteal support. (D) GnRH agonist long protocol. MCD, menstrual cycle day; rFSH, recombinant FSH; hMG, human menopausal gonadotropin; OPU, oocyte pick up; ET, embryo transfer; GnRHa, GnRH agonist.

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first cohort between the conventional and the early GnRH antagonist start cycles. The mean E_2 level on the day of hCG administration (2,737 pg/mL vs. 3,222 pg/mL) and the mean number of retrieved oocytes (11.7 vs. 13.6) and that of mature oocytes (8.8 vs. 10.7) tended to be higher in the modified early GnRH antagonist cycle than in the cycles treated with the conventional GnRH antagonist protocol without any statistical significance. The CPR in the modified early GnRH antagonist start protocol was higher than that in the conventional GnRH antagonist cycles (30.2% vs. 41.2%), which did not reach any statistical significance. The CPR of the modified early GnRH antagonist start protocol was comparable to that of the GnRH agonist long protocol (41.2% vs. 39.7%) (Table 2).

Discussion

Our study assessed starting GnRH antagonist early for the potential inhibition of the interphase increase in the FSH level. In women with regular cycles, follicular recruitment for the next cycle is initiated by

Table 1. IVF outcomes between conventional and early GnRH antagonist start cycles in Cohort I

Characteristic	Conventional GnRH antagonist cycle	Early GnRH antagonist start cycle	*p*-value
No. of attempted cycles	34	34	-
Age (yr)	34.2±3.7	34.1±3.8	NS
Body mass index (kg/m^2)	21.4±2.5	22.3±3.4	NS
Anti-Müllerian hormone (ng/mL)	3.2±2.4	3.6±3.1	NS
Day-3 FSH (IU/mL)	7.5±3.4	7.6±3.2	NS
E_2 on hCG day (pg/mL)	2533.6±1669.4	3432.9±2100.5	NS
COS duration (day)	9.9±1.5	10.7±1.5	NS
Total dosage of gonadotropin (IU)	2894.5±693.1	2916.2±647.0	NS
No. of oocytes retrieved	11.4±7.5	14.4±9.2	NS
No. of mature oocytes retrieved	8.2±6.1	11.9±7.9	0.04
No. of mature oocytes/gonadotropin 100 IU	0.2±0.1	0.4±0.3	NS
Fertilization rate (%)	67.5±27.4	69.5±22.6	NS
No. of embryos transferred	3.0±0.9	3.2±0.9	NS
CPR/ET (%)	32.1 (9/28)	31.0 (9/29)	NS
OHSS, severe (%)	5.9 (2/34)	8.8 (3/34)	NS

Values are presented as mean±SD.
NS, non specific; COS, controlled ovarian stimulation; CPR, clinical pregnancy rate; ET, embryo transfer; OHSS, ovarian hyperstimulation syndrome; severe OHSS, marked abdominal distension with hospital admission.

Table 2. IVF outcomes of embryo-transfer cycles in Cohort II

Characteristic	Conventional GnRH antagonist cycle (A)	Modified early GnRH antagonist cycle (B)	GnRH agonist long protocol cycle (C)	*p*-value
No. of ET cycles	43	34	73	-
Age (yr)	33.1±3.3	33.3±3.2	33.1±2.8	NS
Anti-Müllerian hormone (ng/mL)	3.1±1.9	2.9±2.9	3.9±2.3	NS
Day-3 FSH (IU/mL)	8.1±4.1	8.7±3.0	-	NS
E_2 on hCG day (pg/mL)	2,739.4±2028.5	3,122.0±2,351.8	4,178.2±2262.4	(A)(C) 0.004
COS duration (day)	10.0±3.0	11.1±1.7	11.1±1.6	(A)(C) 0.019
Total dosage of gonadotropin (IU)	2,569.2±1202.2	2,642.6±847.3	2,990.9±783.7	(A)(C) 0.039
No. of oocytes retrieved	11.7±5.8	13.6±8.7	16.2±6.5	(A)(C) 0.003
No. of mature oocytes retrieved	8.8±4.9	10.7±6.0	11.9±5.5	(A)(C) 0.022
No. of mature oocytes/ gonadotropin 100 IU	0.4±0.3	0.5±0.4	0.5±0.3	NS
Fertilization rate (%)	70.3±21.3	76.9±21.1	63.4±20.5	NS
No. of transferred embryos	3.6±2.8	3.4±0.8	3.3±0.7	NS
CPR/ET (%)	30.2 (13/43)	41.2 (14/34)	39.7 (29/73)	NS
OHSS, severe (%)	7.0 (3/43)	11.8 (4/34)	12.3 (9/73)	NS

Values are presented as mean±SD.
NS, non specific; COS, controlled ovarian stimulation; CPR, clinical pregnancy rate; ET, embryo transfer; OHSS, ovarian hyperstimulation syndrome; severe OHSS, marked abdominal distension with hospital admission.

the interphase increase in endogenous FSH secretion. FSH, in turn, stimulates follicular recruitment, and ultimately, the feedback mechanisms between the hypothalamus-pituitary and the ovarian follicles lead to single follicular selection and ovulation, while the other recruited follicles undergo atresia.

The FSH levels begin to increase at the end of the luteal phase of menstrual cycles due to the demise of the corpus luteum and the subsequent decrease in estrogen production [12,14].

In COS, exogenous gonadotropins are administered to assure multifollicular development by rescuing the rest of the follicle cohort from atresia, and the antral follicles are expected to grow in a coordinated fashion in response to exogenous gonadotropins in order to accomplish simultaneous follicular maturation. In the conventional GnRH antagonist cycles, COS was commenced on day 2 or 3 of the menstrual cycles without suppression of the interphase increase in the FSH level. The interphase increase in the FSH level leads to follicular recruitment; then, exogenous FSH administration for COS induces additional follicular growth of the already recruited follicles, while recruiting some other follicles in a less advanced stage of development than the interphase cohort. Then, at the time of hCG administration, several other follicles will not be in synchrony with the follicle cohort recruited during the interphase. The lower oocyte and embryo yield in GnRH antagonist cycles compared with the GnRH agonist long protocol cycles may be considered a limitation of the GnRH antagonist use for COS [2,3].

If the interphase increase in the level of endogenous FSH can be suppressed before COS is started, exogenous gonadotropins may become the sole source of ovarian stimulation, which may result in synchronous follicular development. The present study examined whether early initiation of the GnRH antagonist, starting from menstrual cycle day 2, affects follicular synchronization, favorably leading to increased mature oocyte yield as compared to the conventional antagonist protocol. The interphase increase in FSH is not consistent among women because of its inherent variability. The FSH increase is evident from day 8 to day 18 after the LH peak, and the FSH increase during the early follicular phase is also observed. The FSH level is shown to increase from 4 IU/L to 14 IU/L during the interphase [13]. Therefore, it is difficult to estimate the exact timing of the interphase increase in the FSH level, and it is impossible to identify this entity with a single blood test. We believe that the peak FSH increase will be attained a few days after the onset of FSH increase, which has been observed to occur in the early days of menstruation. Starting the antagonist as early as possible after menses, that is, from menstrual cycle day 2, may prevent the peak FSH increase in the recruited follicular cohort.

The results from Cohort I indicated that the mean number of oocytes was significantly higher and the proportion of metaphase II oocytes was significantly increased from 71.9% to 82.6% in the early GnRH antagonist start cycles when compared to the conventional antagonist cycles. This reflects a more coordinated follicular growth, possibly resulting from the improved homogeneity of antral follicles with endogenous FSH suppression by early antagonist initiation. The increased duration of ovarian stimulation may result from a longer growth course of antral follicles not primed with the interphase increase in the FSH level. A few previous reports have shown the beneficial effects of early antagonist administration. Early follicular-phase GnRH antagonist start on day 3 was reported to improve the meiotic status and the competence of the retrieved oocytes [15].

By using the early GnRH antagonist start protocol, we expected better pregnancy outcomes as compared to the conventional GnRH antagonist protocol due to the LH suppression induced by the early GnRH antagonist administration [16,17]. In the conventional antagonist cycles, the LH levels remain unsuppressed and the E_2 production is enhanced during the early follicular phase [16]. High exposure to LH and E_2 in the early follicular phase has been related to suboptimal reproductive outcomes [17], indicating that the lower LH and E_2 levels induced by the early antagonist administration may have a positive effect on the IVF outcomes.

However, our initial cohort failed to show better pregnancy rates in the early GnRH antagonist start cycles despite an increased mature oocyte yield as compared to the conventional antagonist protocol. With the early initiation of the GnRH antagonist, the LH level is believed to be very low. Cetrorelix acetate has been shown to induce a rapid, transient, and dose-dependent decrease in endogenous gonadotropins that is faster and more pronounced for LH than for FSH [18]. Kolibianakis et al. [19] reported a significant drop in the LH level after early antagonist initiation starting on day 2 of the menstrual cycle. The basal LH level of 4.8 IU/L was decreased to 1.0 IU/L after the GnRH antagonist start, and thereafter, the LH levels remained low during the stimulation [19]. Prolonged use of the GnRH antagonist may actually result in profound LH suppression, which could affect the IVF outcome unfavorably.

In Cohort II, by switching rFSH to HP-HMG on day 5 of the stimulation, the CPR was increased compared with the conventional antagonist cycles by 10%; however, this increase was not statistically significant.

HP-HMG has both FSH and LH activities in a 1:1 ratio and most of its exogenous LH activity derives from HCG rather than from the LH content [20]. The use of HP-HMG during ovarian stimulation following LH suppression is supposed to indirectly increase the embryo quality and/or the endometrial receptivity by combining the HCG-driven LH activity with the FSH activity [21-23]. LH activity supplementation in combination with FSH during COS may lower the gradual increase in the P4 levels observed during COS. The increased P4

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levels detected during the COS before hCG administration have been associated with a lower clinical pregnancy outcome, possibly due to decreased endometrial receptivity induced by early exposure to P4 [24,25]. An important weakness of our study is the lack of information on the LH and P4 levels during COS, particularly from Cohort II.

In the modified early GnRH antagonist start protocol, the GnRH agonist was also administered as an adjunct to LPS. GnRH and its receptors have been found in extra-pituitary tissues such as those of the endometrium and embryo. GnRH analogs may also exert direct actions in these tissues, and some authors have raised concerns about the adverse effects of the antagonists through these extra-pituitary target tissues [26]. We used the GnRH agonist addition to LPS in the modified early antagonist start cycles, which may be an additional factor for improved CPR as compared to the conventional antagonist cycles. Further, the improved CPR in the Cohort II results from HP-HMG switched from rFSH or GnRH agonist addition to LPS should be evaluated by a further study.

Since we were interested in a more patient-friendly approach to using the GnRH antagonist while maximizing the outcomes, the modified early GnRH antagonist start protocol may constitute an attractive alternative to the conventional antagonist protocols. The modified early GnRH antagonist start protocol has an additional advantage over the previously attempted pretreatment strategies. First, this protocol can be commenced during the current menstrual cycle without waiting for the next cycle or without needing induced withdrawal bleeding. Secondly, this protocol may improve the early follicular endocrine environment by lowering the LH level, and LH support is provided when it is needed by HP-HMG. Third, early antagonist administration can prevent earlier LH surges in some select patients. However, our analysis did not achieve a significantly higher CPR. The retrospective nature of the study is one of its weakness, and our findings need validation by prospective randomized clinical trials.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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