

GnRH Antagonist Protocol: Is It Effective for Expected Poor Ovarian Responders with Tubal Factor Undergoing IVF?

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Abstract

Background: This study aimed to determine if the gonadotropin releasing hormone (GnRH) antagonist protocol is optimal for expected poor ovarian responders with tubal factor undergoing *in vitro* fertilization-embryo transfer (IVF-ET). **Methods:** A total of 341 IVF-ET cycles were retrospectively identified. The following inclusion criteria were applied: age ≥ 40 years and patients with tubal factors. The cycles were divided into two groups: a GnRH antagonist group (157 cycles) and a GnRH agonist group (184 cycles). **Results:** The duration of stimulation and the total doses of gonadotropin in the GnRH agonist group were significantly more than those in the GnRH antagonist group ($P < 0.05$). There were significant differences in LH and P values on the hCG measurement days between the two groups (0.91 ± 1.17 vs. 4.82 ± 4.69 U/L and 0.69 ± 0.42 vs. 1.03 ± 0.50 ng/mL, $P < 0.05$). The implantation rate of the GnRH antagonist group was 12.24%, which was slightly higher than that of the GnRH agonist group (10.10%, $P = 0.437$). The clinical pregnancy rate of the two groups showed no statistical differences (23.36% vs. 23.03%, $P = 1.000$). **Conclusion:** For expected poor ovarian responders, the GnRH antagonist protocol was, to some extent, superior to the GnRH agonist protocol in terms of the implantation and clinical pregnancy rates.

Keywords

Poor Ovarian Responders, GnRH Antagonist Protocol, GnRH Agonist Protocol

1. Background

During controlled ovarian stimulation (COS) for assisted reproductive technologies (ARTs), poor ovarian response (POR) to gonadotropin (Gn) stimulation is

not uncommon [1]. The incidence of POR has been reported to vary between 9% and 24% [2]. In 2011, the Bologna criteria for POR were raised and have been recently recognized. According to the Bologna criteria, POR should be diagnosed if the patients have two out of the following three features: 1) advanced age (≥ 40 years) or any other risk factor for POR; 2) a history of POR (three or fewer oocytes retrieved with ovulation induction); or 3) lower ovarian reserve [antral follicular count (AFC) less than 5 - 7 follicles or Anti-Mullerian hormone (AMH) level less than 0.5 ng/mL to 1.1 ng/mL] [3].

Gonadotropin-releasing hormone (GnRH) agonists have been successfully used for the last 20 years [4]. Hypophyseal desensitization can be induced by the administration of GnRH agonists, which can prevent premature luteinization and then significantly reduce the cycle cancellation rate via the nearly complete inhibition of spontaneous LH surges ($< 2\%$) [5]. Because the long protocol of GnRH agonists has been found to be superior to other protocols, it is most frequently used throughout the world. However, for POR, extremely higher doses of Gn and longer durations of stimulation are often required due to over-suppression [6]. The cycle cancellation rate is also fairly high for POR with the GnRH agonist long protocol.

For POR, selecting an optimal protocol for IVF/ICSI cycles is still a frustrating challenge. Numerous strategies have been suggested to improve the outcome of POR, such as the GnRH antagonist (GnRHant) protocol, minimal ovarian stimulation protocol, Shanghai protocol, and so on [1] [7] [8] [9]. The GnRHant protocol, which was first introduced in the late 1990s, may be an effective protocol for POR because of its distinctive pharmacologic properties. Currently, GnRH antagonists are mainly used in many clinics for patients with PCOS undergoing IVF. However, even though it can significantly lower the incidence of OHSS, the lower implantation and pregnancy rate limit the application of the GnRHant protocol.

There is still no consensus on which protocol is the most effective and safe one for POR. The aim of this study was to compare the effectiveness of the GnRHant protocol and GnRH agonist long protocol in expected POR with tubal factor during IVF cycles.

2. Method

A total of 341 IVF-ET cycles from January 2011 to December 2014 were retrospectively identified in the Center for Reproductive Medicine of Sun Yat-sen Memorial Hospital of Sun Yat-sen University. The following inclusion criteria were applied: 1) age ≥ 40 years; and 2) patients with tubal factors. The cycles were divided into two groups accordingly: a GnRHant group (157 cycles) and a GnRH agonist group (184 cycles). This retrospective study was approved by the Sun Yat-sen Memorial Hospital Medicine Ethics Committee. Patient records and information were anonymized and de-identified prior to analysis.

In the GnRHant group, the protocol was the same as previously described [10].

Ovarian stimulation commenced with 150 - 450 IU rFSH from day 2 to 3 of the menstrual cycle. When the serum E₂ level was higher than 300 pg/mL, or a lead follicle reached a mean diameter of 14 mm, a daily dose of 0.25 mg GnRHant (Cetrotide, Serono, Switzerland) was initiated and continued until the day of hCG administration. When at least two follicles reached a mean diameter of 18 mm, recombinant hCG (Serono, Switzerland) was given to trigger follicle maturation. Oocyte retrieval was performed transvaginally 34 - 36 hours later.

In the GnRHa group, down-regulation treatment with 1.0 - 1.3 mg of Triptorelin (3.75 mg Gonapeptyl; Ferring) was started from day 20 of the preceding menstrual cycle. In accordance with body mass index and patient age, recombinant FSH (Gonal-F, Serono, Switzerland) and/or hMG (Li Zhu, China) were used at dosages ranging between 150 IU/day and 450 IU/day. The timing of the hCG trigger was similar to the GnRH agonist protocol. Oocyte retrieval was carried out 34 - 36 hours after triggering by transvaginal ultrasound-guided puncture.

The embryo transfers (ET) were performed three to five days later under ultrasound guidance. The thickness of the endometrium less than 6 mm was considered too thin. The cycles were cancelled when the endometrium was too thin or there were no dominant follicles (diameter less than 14 mm). Pregnancy was diagnosed by an increase in the concentration of serum β -hCG, which was tested 14 days after ET. Clinical pregnancy was defined as the presence of a gestational sac on vaginal ultrasound examination. Miscarriage was defined as a pregnancy loss before 28 weeks [11].

3. Statistical Analysis

SPSS statistical software package (version 11.0) was used for statistical analysis. Values are expressed as the mean \pm SD. The unpaired Student's *t*-test was used to compare means from two groups. The χ^2 -test was used to compare categorical variables. *P* < 0.05 was considered statistically significant.

4. Results

A total of 341 IVF-ET cycles were retrospectively studied. The patient demographic variables are compared in **Table 1**. The two groups were similar in terms of age, basal FSH, body mass index, proportion of primary infertility, and duration of infertility. The duration of stimulation and the total doses of Gn in the GnRHa group were 11.51 ± 1.46 days and 3317.34 ± 775.29 IU, respectively, which were significantly more than those in the GnRHant group (9.70 ± 2.23 days and 2306.88 ± 757.22 IU, *P* < 0.05). There were significant differences in LH and P levels on the hCG day between the two groups (0.91 ± 1.17 vs. 4.82 ± 4.69 U/L and 0.69 ± 0.42 vs. 1.03 ± 0.50 ng/mL, *P* < 0.05). However, the E₂ levels on the hCG day were similar between the two groups (2095.28 ± 1213.17 vs. 1953.47 ± 1248.00 pg/mL, *P* = 0.361).

As shown in **Table 2**, the number of oocytes retrieved in the GnRHant group was 6.37 ± 4.26 , which was significantly less than the number retrieved in the

Table 1. Epidemiologic and stimulation characteristics.

Variable	GnRHa (N = 184)	GnRHant (N = 157)	P value
Age (years)	41.52 ± 1.56	41.48 ± 1.66	0.781
Basal FSH (IU/L)	10.16 ± 4.87	11.17 ± 6.34	0.198
Body mass index (kg/m ²)	22.40 ± 2.48	22.38 ± 3.23	0.953
Proportion of primary infertility (%)	34.87%	31.78%	0.645
Duration of infertility (years)	6.78 ± 4.77	6.21 ± 5.12	0.353
Duration of stimulation (days)	11.51 ± 1.46	9.70 ± 2.23	<0.05
Total dose of Gn administered (IU)	3317.34 ± 775.29	2306.88 ± 757.22	<0.05
E ₂ level on hCG trigger day (pg/mL)	2095.28 ± 1213.17	1953.47 ± 1248.00	0.361
LH level on hCG trigger day (mIU/mL)	0.91 ± 1.17	4.82 ± 4.69	<0.05
P level on hCG trigger day (ng/mL)	0.69 ± 0.42	1.03 ± 0.50	<0.05
Endometrial thickness on hCG trigger day (mm)	10.89 ± 2.47	10.39 ± 2.35	0.099

Note: NS = not statistically significant. Values presented as mean ± SD unless otherwise specified.

Table 2. IVF outcomes.

Variable	GnRHa (N = 184)	GnRHant (N = 157)	P value
No. of oocytes retrieved	10.38 ± 5.71	6.37 ± 4.26	<0.05
No. of cancelled fresh transferred cycle (n, %)	32/184 (17.39%)	50/157 (31.85%)	<0.05
No. of cancelled fresh transferred cycle because of no dominant follicles (n, %)	11/32 (34.38%)	12/50 (24%)	0.325
Implantation rate (%)	10.10%	12.24%	0.437
Clinical pregnancy/fresh transferred cycle (n, %)	35/152 (23.03%)	25/107 (23.36%)	1.000
Miscarriage/fresh transferred cycle (n, %)	13/35 (37.14%)	9/25 (36.00%)	1.000

Note: Values presented as mean ± SD unless otherwise specified.

GnRHa group (10.38 ± 5.71, $P < 0.05$). However, the numbers of high quality embryos and transferred embryos were similar in two groups (2.21 ± 1.65 vs. 2.17 ± 1.54, 2.09 ± 0.65 vs. 2.03 ± 0.33). In the GnRHa group, the rate of cancelled freshly transferred cycles was 17.39%, which was significantly lower than that in the GnRHant group (31.85%, $P < 0.05$). The rate of cancelled freshly transferred cycles because of no dominant follicles in the GnRHa group was slightly higher than that in the GnRHant group (34.38% vs. 24%, $P = 0.325$).

When the χ^2 -test was performed, we obtained the following results: 1) The implantation rate of the GnRHant group was 12.24%, which was slightly higher than that of the GnRHa group (10.10%, $P = 0.437$); 2) there was no difference of the clinical pregnancy rate between two groups (23.36% vs. 23.03%, $P = 1.000$);

and 3) there was no significant difference in the miscarriage rate between the two groups (36.00% vs. 37.14%, $P = 1.000$).

5. Discussion

Many studies demonstrated that, in poor ovarian responders with declining ovarian reserve, the expected pregnancy rate was dramatically lower than that of younger women [12]. The frequency of poor ovarian responder status has been estimated to be 10% in the general population and markedly higher in patients over 40 years of age [13]. For these patients, selection of an effective protocol remains a frustrating challenge in IVF cycles. The GnRH agonist protocol has been widely used in IVF centers. However, there are several disadvantages for the application of the GnRH-agonist long protocol in low responders, including increased Gn doses, the longer duration of Gn administration [14], the higher cycle cancellation rate, and the increased treatment costs [15]. Numerous strategies have been attempted to improve the outcome of POR, including: 1) increasing the doses of Gn [16]; 2) application of other protocols [17]; 3) addition of growth hormone (GH), and 4) addition of growth hormone-releasing factor (GHRF) [18].

However, most of these interventions have achieved extremely limited advantages; consequently, the optimal protocol for POR is still unknown [6]. The introduction of GnRH antagonists presented hope for POR. GnRH antagonists can induce pituitary suppression within a few hours without a “flare-up” effect, and the suppression can be released immediately after their discontinuation [19]. In the present study, we investigated the effectiveness of the GnRH antagonist protocol in expected poor ovarian responders. We found that the duration of stimulation and the total doses of Gn in the GnRH_a group were 11.51 ± 1.46 days and 3317.34 ± 775.29 IU, which were significantly more than those in the GnRH_{ant} group (9.70 ± 2.23 days and 2306.88 ± 757.22 IU, $P < 0.05$). These were in keeping with the results of previous studies. Several studies demonstrated a lower implantation rate and pregnancy rate in the GnRH-ant protocol, which limited its wide application [20]. However, our study showed that, for expected POR (age ≥ 40 years), the implantation rate and clinical pregnancy rate of the GnRH_{ant} group were slightly higher than those in the GnRH_a group (12.24% vs. 10.10%, $P = 0.437$; 23.36% vs. 23.03%, $P = 1.000$). In our previous study, we demonstrated that, for potentially high responders, the GnRH_a protocol was superior to the GnRH_{ant} protocol in terms of normal fertilization rate, implantation rates, and clinical pregnancy rates [10]. These findings showed that the GnRH_{ant} protocol may be an optimal protocol for expected poor ovarian responders, but not for potentially high responders.

There were some limitations because it was a retrospective study. The small sample size of the study should be noted. Our results should be confirmed by further, adequately sized studies, or meta-analyzed along with similar studies.

6. Conclusion

In conclusion, our study demonstrated that for expected poor ovarian responders, the GnRH antagonist protocol was, to some extent, superior to the GnRH agonist protocol in terms of the duration of stimulation, the total doses of Gn, the implantation rates and clinical pregnancy rates.

Competing Interests

The authors declare that they have no competing interests.

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