

Comparison between GnRH Antagonist and Agonist Long Protocols in Poor Responders

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불량반응군에서 GnRH Antagonist와 Agonist Long Protocol의 비교

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목 적: 본 후향적 연구는 성선자극호르몬분비호르몬 작용제 (gonadotropin-releasing hormone [GnRH] agonist)와 길항제 (GnRH antagonist) 치료를 받은 불량반응군의 결과를 비교, 분석하고자 하였다.

연구방법: 총 172회의 체외수정시술 주기에서 GnRH agonist 또는 antagonist protocol로 과배란유도를 시행받고 채취된 난자의 수가 5개 미만인 불량반응군을 대상군으로 하였다. 난포 및 채취된 난자의 수, 수정률 등의 결과를 두 군 간에 비교하였다.

결 과: GnRH agonist long protocol과 antagonist protocol 두 군 간에 난포 및 난자의 수와 수정률은 차이를 보이지 아니하였다. 반면, 과배란유도 제7/8일의 혈중 E₂ 농도는 GnRH antagonist군에서 더 높았던 반면, 사용한 평균 성선자극호르몬의 용량은 유의하게 적고 과배란유도 기간은 짧은 것을 확인할 수 있었다 (각각 $p < 0.01$).

결 론: 불량 반응군에서 GnRH agonist long protocol에 비하여 GnRH antagonist protocol의 경우 노력이 상대적으로 적게 필요한 반면 비슷한 임상적 결과를 고려할 때, GnRH antagonist protocol이 상대적으로 우수한 것으로 생각된다.

[Korean. J. Reprod. Med. 2010; 37(3): 239-244.]

중심단어: 불량반응군, GnRH 작용제, GnRH 길항제, 과배란유도, 체외수정시술

The term "poor responder" has been introduced to describe basically a group of patients who yield not

enough oocytes even after controlled ovarian hyperstimulation. Although no consensus has been made as to what the term "poor responder" exactly should mean, several stimulation methods have been suggested for poor responders, and some of the options are as follow: increment of daily dose of gonadotropins; administration of luteinizing hormone (LH) in the early phase of folliculogenesis; application of modified gonadotropin-releasing hormone (GnRH) agonist protocols such as

접 수 일: 2010년 5월 17일, 수정일: 2010년 9월 1일

게재확정일: 2010년 9월 8일

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*This study was supported by a grant of the Korea Health 21 R&D Project, Ministry of Health & Welfare, Republic of Korea (01-PJ10-PG6-01GN13-0002).

microdose flare-up protocol as well as GnRH antagonist in various protocols.¹⁻³

Although it would be ideal for clinicians to be able to predict poor responders before the first *in vitro* fertilization (IVF) cycle, it is almost impossible to do so. Therefore, in general, most centers begin the first IVF cycle with either GnRH agonist or GnRH antagonist. Even if the patient is presumed to be a poor responder, either GnRH agonist or GnRH antagonist is used in the first cycle. Only after the first IVF cycle, is the poor responder diagnosed as one. Despite some reports that supported the use of GnRH antagonist for poor responders with favorable outcome, no recent literature has attempted to show direct comparison in poor responders between GnRH agonist long and GnRH antagonist protocol, except for one small-sized randomized controlled trial.⁴

Therefore, it would be meaningful to investigate which protocol would be advantageous in poor responders undergoing assisted reproductive technology (ART). We aimed to assess which IVF protocol may yield favorable outcome in poor responders, retrospectively.

MATERIALS AND METHODS

1. Patients and study design

A total of 172 cycles were included in this study from Jan 2005 through Jan 2009. Poor responder was defined as less than or equal to five oocytes retrieved, regardless of the result of the previous cycle. All the patients who were enrolled had one or more cycles of less than or equal to five oocytes retrieved in their controlled ovarian hyperstimulation and IVF/intracytoplasmic sperm injection attempts with either GnRH agonist long protocol or GnRH antagonist protocol. The enrolled patients had been applied with various number of cycles varying from one cycle to as many as nine cycles. The poor responders were retrospectively divided into two groups according to the protocols they had undergone.

2. Controlled ovarian hyperstimulation and patient procedures

GnRH agonist long protocol group was composed of the patients who were injected with GnRH agonist triptorelin (Decapeptyl[®], 0.1 mg/d; Ferring, Malmö, Sweden) during the mid-luteal phase of the previous cycle, then, gonadotropin was added on cycle day 2 or 3 and continued till the day before human chorionic gonadotropin (hCG) administration. When the follicles reached 17~18 mm in their largest diameter, gonadotropin injection was discontinued, and hCG was given at 34~36 hours before ultrasonography-guided transvaginal oocyte retrieval. Peak E₂ and progesterone levels were measured on the day of hCG administration.

The other group was GnRH antagonist group, and gonadotropin was given on cycle day 2 or 3 and continued till the day before the hCG administration day. When the mean diameter of the leading follicle reached 14 mm on ultrasonography, 0.25 mg Cetrotide[®] (Serono, Geneva, Switzerland) was administered daily till the hCG administration day. When the follicles reached 17~18 mm in their largest diameter, gonadotropin was discontinued, and either recombinant hCG 250 µg or urinary hCG 10,000 IU was given. Oocyte retrieval and embryo transfer was performed in same fashion as that of GnRH agonist long protocol.

As many as four embryos were transferred 2 to 3 days after oocyte retrieval. Each embryo was evaluated and rated upon their morphologies and cleavage rates. The luteal phase support was provided either with progesterone in oil (Progest[®], 50 mg; Samil, Seoul, Korea) or with 8% progesterone gel (Crinone[®], Serono, Miami, FL, USA) for 14 days beginning on the day of transvaginal oocyte retrieval. Then, the luteal phase support was continued for 6~8 weeks when pregnancy was confirmed. Serum β-hCG was drawn to confirm the pregnancy result 14 days after the day of oocyte

Table 1. Demographic data and endocrine variables of the study groups

	GnRH agonist group (n=92)	GnRH antagonist group (n=80)	<i>p</i> -value
Age (yr)	36.3±4.0	35.6±4.8	0.36
Age of partner (yr)	38.3±6.1	38.3±6.0	0.99
Infertility factors			
Male factor (%)	43.5	37.5	0.25
Uterine factor (%)	26.0	16.3	0.25
Tubal factor (%)	29.3	33.8	0.25
Ovulatory factor (%)	47.8	51.3	0.25
Peritoneal factor (%)	13.0	6.3	0.25
Unexplained (%)	15.2	25.0	0.25
Infertility duration (yr)	4.8±3.4	4.5±3.1	0.57
BMI (kg/m ²)	22.4±4.0	22.0±4.7	0.56
Basal FSH (mIU/mL)	6.2±4.6	8.6±11.8	0.13
Basal E ₂ (pg/mL)	44.0±34.9	48.8±56.9	0.57
AFC	7.5±4.6	7.6±6.1	0.90

Data are presented as mean±SD.

GnRH, gonadotropin-releasing hormone; BMI, body mass index; FSH, follicle-stimulating hormone; E₂, estradiol; AFC, antral follicle count.

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retrieval, and later clinical pregnancy was identified by the confirmation of intrauterine gestational sac with fetal heartbeats at 3~4 weeks after the day of oocyte retrieval.

3. Statistical analyses

Data are expressed as the mean ± SD or percentages, unless otherwise indicated. Statistical analysis was performed by using the Pearson's χ^2 test for categorical variables, and Student's *t*-test for continuous variables, as necessary. All statistical analyses were performed by using SPSS software, version 12.0 for Windows (SPSS Inc., Chicago, IL, USA). *P*-value of < .05 was considered statistically significant.

RESULTS

Ninety-two cycles were applied with the GnRH agonist long protocol, and 80 cycles were applied with the GnRH antagonist protocol. Demographic data and infertility factors between the two study groups were shown to be similar (Table 1).

Serum E₂ level on Day 7/8 was higher in GnRH antagonist group, whereas mean dosage of gonadotropin (ampules) required as well as the number of days of stimulation were shown to be higher in GnRH agonist group. The level of E₂ and endometrial thickness on the day of hCG administration, the number of oocytes retrieved and the number of embryos transferred showed no difference between the two groups. The fertilization

Table 2. Cycle characteristics and fertilization rate, embryological data of the study groups

	GnRH agonist group (n=92)	GnRH antagonist group (n=80)	p-value
Day 7/8 E ₂ (pg/mL)	124.8±134.1	268.3±189.0	<0.01
No. of ≥16 mm-sized follicles, Rt.	1.2±1.2	1.2±1.3	0.89
No. of ≥16 mm-sized follicles, Lt.	1.3±1.3	1.1±1.1	0.33
Mean gonadotropin dose (ampule)	42.5±15.0	31.9±17.9	<0.01
Duration of stimulation (day)	10.0±1.8	8.5±2.6	<0.01
E ₂ on the day of hCG administration	885.6±743.1	858.0±568.2	0.82
EMT (mm) on hCG day	10.7±2.5	10.6±2.8	0.83
No. of oocytes retrieved	3.3±1.4	3.1±1.5	0.45
No. of embryos transferred	2.3±1.0	2.2±1.2	0.75
CES	45.4±27.4	50.6±29.0	0.40
CES/no. of embryos	19.2±8.4	21.0±8.1	0.32
Fertilization rate (%)	48.4	56.5	0.12

Data are presented as mean±SD or percentile.

1 amp = 75 IU.

GnRH, gonadotropin-releasing hormone; E₂, estradiol; EMT, endometrial thickness; CES, cumulative embryo score.

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rate of the two groups did not show statistically significant difference (Table 2).

DISCUSSION

Poor ovarian response is usually defined as reduced follicle/oocyte production after controlled ovarian hyperstimulation, however, consensus has yet to be reached on this definition. Some of the criteria used to define poor responders are the numbers of mature follicles noted on ultrasonography, varying from less than five to less than two, elevated early follicular phase serum FSH levels with minimum values ranging from 6.5 to 15 mIU/mL, etc.^{5,6} Many factors have been known to contribute to such poor ovarian response, and they include age of the patients, endometriosis, previous ovarian surgery, basal hormonal status, etc.

There are several ways to predict poor responders prior to any trial of IVF protocol and they are basal FSH level, estradiol level, clomiphene challenge test, inhibin, anti-mullerian hormone, ultrasonographic evaluation of small antral follicles in early follicular phase.^{7~13}

Even if all the above mentioned tests are performed, it is impossible to completely predict poor responders. Therefore, we are faced with the trouble of having to go through 2~3 IVF cycles in order for us to predict poor responders with certainty. Since, usually GnRH agonist or GnRH antagonist protocols are applied as the first protocol, it would be meaningful to see which protocol is more beneficial. Many prospective and retrospective studies have proven advantages of GnRH antagonist, such as lower requirements of gonadotropin, shorter duration of stimulation, reduction in costs, less waiting time between cycles, and avoidance of hypoestrogenic

side effects associated with prolonged use of GnRH agonists.^{14~16} In our study, the GnRH antagonist cycles showed similar advantages such as similar fertilization rate, lower requirements of gonadotropin, and shorter duration of stimulation days.

Previously, there is one randomized controlled study that asserted the superiority of GnRH antagonist protocol over the standard GnRH agonist long protocol in poor responders. The study concluded that GnRH antagonist protocol group showed improved response with fewer doses of gonadotropin as well as shorter duration of stimulation, thus proving it to be more favorable protocol than standard GnRH agonist long protocol.⁴ However, there is a clear difference between this randomized controlled study and our study. In the previous study, the total number of subjects was small with 30 patients, the mean age of the patients was relatively old, and the criteria of poor responder were different.

One of the limitations of this study is that the individual physician chose whether the GnRH agonist long or the GnRH antagonist protocol was used based on their preference. Thus, the heterogeneity of the patients may be the weakness of our study. However, the two patient groups had similar baseline characteristics, which make it possible to compare the outcomes between the two groups with a certain degree of significance. Also, our study included a total of 172 cycles, which empowers the significance of our data. Secondly, most of our study patients were not known poor responders. Most of the patients that have been categorized as poor responders in this study had not showed poor response in their previous attempts with IVF protocols, but rather, they were newly recognized poor responders. Some of the patients were in their very first attempt of ART with no abnormal finding, thus making it difficult for us to predict their outcome. Some of the possible reasons that may have contributed to such poor response are missed optimal timing of oocyte retrieval, technical error during

oocyte retrieval procedure, or even poor compliance. A few patients had actually missed their visiting days owing to their own personal matters, and also had cancelled quite a few cycles. Because of its retrospective nature, the gonadotropin dosage might be different according to protocols in our study. However, the patients were given the same range of the starting dose of gonadotropin based on their age or previous response to begin with, which strengthens our results.

In conclusion, our retrospective study attempted to compare the efficacy of GnRH agonist long and GnRH antagonist protocols in poor responders, and the similar outcome despite less effort needed in GnRH antagonist protocol group proved it to be preferable.

Acknowledgement

The authors would like to express our deepest gratitude to Sun Kyung Oh, Hee Sun Kim, Moon Ju Kang, Sung Ah Kim for their laboratory support of this study.

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= Abstract =

Objective: The objective of this retrospective study was to compare the *in vitro* fertilization (IVF) outcomes of gonadotropin-releasing hormone (GnRH) agonist and GnRH antagonist protocols in poor responders.

Methods: A total of 172 cycles in subjects with less than 5 oocytes retrieved treated with either GnRH agonist long protocols or antagonist protocols were included. The outcome variables such as numbers of growing follicles and retrieved oocytes, and the fertilization rate were evaluated as the main outcome measures.

Results: There was no difference in regard to the numbers of growing follicles and oocytes, and fertilization rate between the two groups. E₂ level on Day 7/8, mean gonadotropin dose, and the days of stimulation were shown to be statistically different ($p < 0.01$, respectively).

Conclusion: Considering that similar results were observed with less time and gonadotropin dose, GnRH antagonist protocol may be considered as a preferable choice over GnRH agonist protocols in poor responders.

Key Words: Poor responder, Gonadotropin-releasing hormone agonist, GnRH antagonist, Controlled ovarian hyperstimulation, *in vitro* fertilization
