



EFFECT OF ORAL GnRH ANTAGONIST RELUGOLIX ON BLOOD HORMONE AND OOCYTE RETRIEVAL - A STUDY OF THE METHOD OF RELUGOLIX ADMINISTRATION

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OBJECTIVE

The GnRH antagonist protocol is one of the most selected methods of controlled ovarian stimulation in assisted reproductive technology. Cetrorelix and Ganirelix are used worldwide to suppress premature LH surge in GnRH antagonist protocol. In Japan, relugolix has been released as an oral treatment for uterus myoma in March 2019, and expected to prevent premature LH surge in controlled ovarian stimulation due to its mechanism of action. This oral GnRH antagonist greatly reduces patient's distress economically, physically and mentally, due to the painless of injection. In the present study, we compared the blood hormone levels, number of oocytes retrieved, and culture results of those using relugolix with those adopting the more conventional method using cetrorelix.

SUBJECT

From December 2010 to February 2021, 251 cycles [214 cycles in the cetrorelix (C) group and 37 cycles in the relugolix (R) group] of ovarian stimulation using GnRH antagonists were included in the study.

METHODS

Ovarian stimulation was started by the third day of the menstrual cycle in all patients. The dosage of gonadotropins was selected based on the patient's age and an assessment of ovarian function reserve as estimated by antral follicle count and anti-Mullerian hormone (AMH) levels. When the follicle diameter reached about 14mm, GnRH antagonists were administered daily. Final oocyte maturation was triggered with GnRH agonist when the largest follicle attained diameter of 18mm. Oocyte retrieval was performed under transvaginal ultrasound guidance 36 hours after GnRH agonist administration. The hormonal profiles were assessed in every patient on the day of ovarian stimulation initiation and 2 days before oocyte retrieval.

RESULTS

Table1. Comparison of the patient background, hormone levels of 2 days before oocyte retrieval and the number of oocytes retrieved in the group C and R.

	Group C (n=214)	Group R (n=37)	P value
Age	32.5±3.4	33.1±3.1	0.413
AMH (ng/ml)	9.0±7.6	6.6±3.6	0.06
Total HMG/FSH doses	1225.3±254.7	1290.5±481.4	0.249
P ₄ (ng/ml)	1.0±0.5	0.4±0.2	<0.01
E ₂ (pg/ml)	2699.8±1988.5	1992.1±1080.4	0.027
LH (mIU/ml)	1.5±2.7	1.1±1.1	0.376
Number of oocytes retrieved	14.1±7.4	8.1±6.6	<0.01
Mature oocyte rate (%)	81.6	80.1	0.692

There were no significant differences in age, AMH, and total HMG/FSH doses among the both groups. The P₄ and E₂ were significantly lower in the group R than in the group C. The number of oocytes retrieved was significantly fewer in the group R than in the group C.

EXAMINATION1

Using the E₂ level per oocyte retrieval in group C as a standard, group R was divided into groups below the standard (group RB) and above the standard (group RA), and blood hormone levels, number of oocytes retrieved, and culture results were compared. The E₂ level per oocyte retrieval in group C was 257.0pg/ml (75 percentile value).

RESULTS

Table2. Comparison of the patient background, the hormone levels of 2 days before oocyte retrieval and the number of oocytes retrieved in the group C, RB and RA.

	Group C (n=214)	Group RB (n=17)	Group RA (n=20)
Age	32.5±3.4	33.6±2.9	32.7±3.3
AMH (ng/ml)	9.0±7.6	7.2±4.2	6.1±3.1
Total HMG/FSH doses	1225.3±254.7	1367.6±631.7	1225.0±324.6
P ₄ (ng/ml)	1.0±0.5 ^a	0.5±0.2 ^b	0.4±0.2 ^c
E ₂ (pg/ml)	2699.8±1988.5	2098.3±871.5	1901.9±1246.3
LH (mIU/ml)	1.5±2.7	1.2±1.3	1.0±0.9
Number of oocytes retrieved	14.1±7.4 ^d	12.7±6.2 ^e	4.2±3.8 ^f
Mature oocyte rate (%)	81.6	86.9	72.9

There were significant differences among a and b, a and c (p <0.01).
There were significant differences among d and f, e and f (p <0.01).

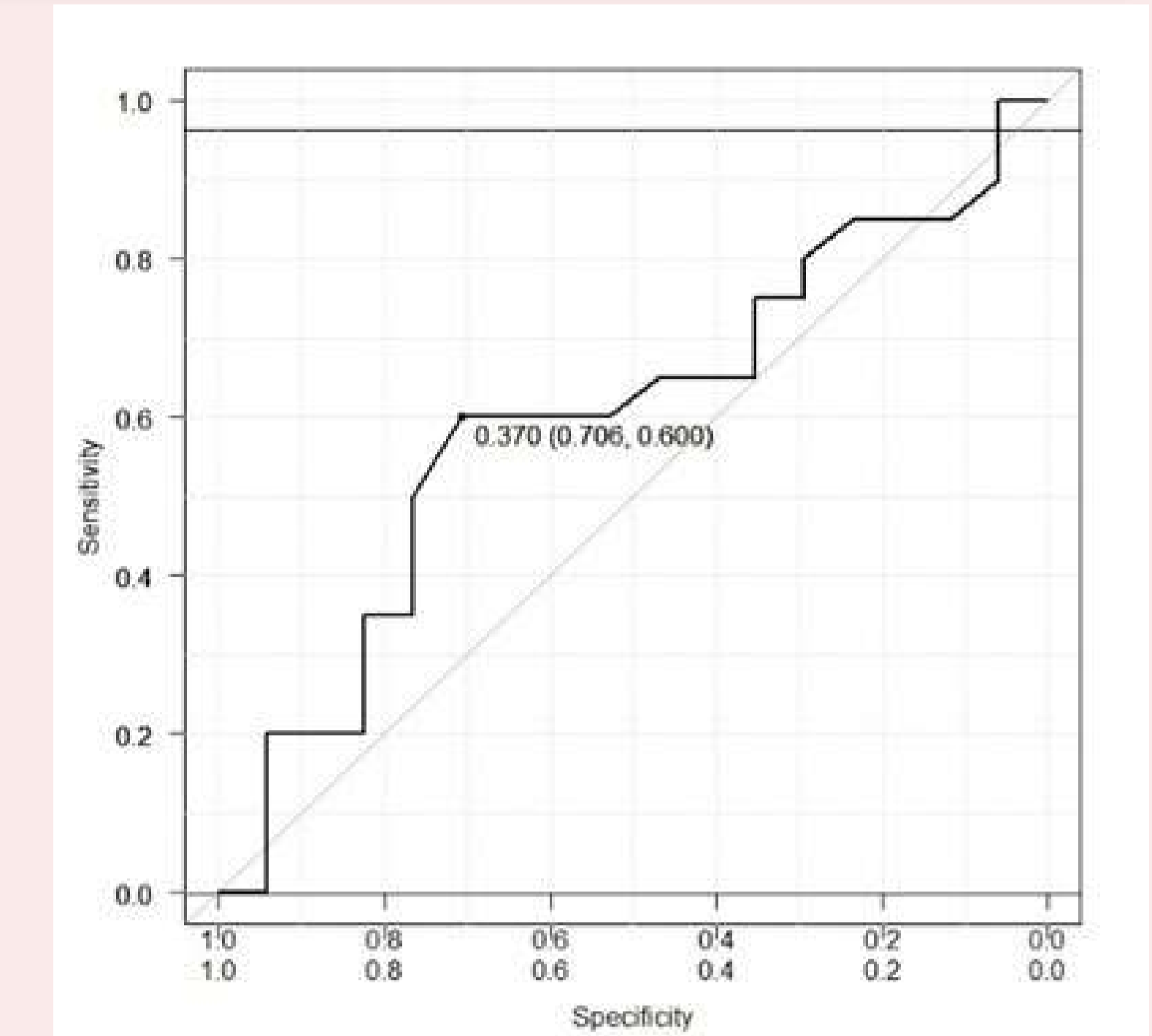
Table3. Comparison of the culture results in the group C, RB and RA.

	Group C (n=214)	Group RB (n=17)	Group RA (n=20)
Fertilization rate (%)	79.5	83.9	87.2
Cleavage rate (%)	96.6	97.6	100
Good blastocyst rate (%)	50	55.2	42.5

There were no significant differences in age, AMH, and total HMG/FSH doses among the group C, RB, and RA. The P₄ levels of 2 days before oocyte retrieval were significantly lower in the group RB and RA than in the group C. The number of oocytes retrieved was significantly fewer in the group RA than in other groups (Table2). Premature ovulation was observed in one case each in the group C and RA. There was no significant difference in fertilization rate, cleavage rate, and good blastocyst rate among all groups (Table3).

EXAMINATION2

A result of examination1 suggested the possibility that the P₄ level was related to decrease of the number of oocytes retrieved. Then ROC curve was drawn from the P levels of the group R, and the cutoff value (0.37) was calculated. Applying this value to the group R, we compared the number of oocytes retrieved, the E₂ level and the culture results of the group below 0.37 and above 0.37.



RESULTS

Table4. Comparison of the E₂ levels and the number of oocytes retrieved in the group below 0.37 and above 0.37.

	Group below 0.37 (n=14)	Group above 0.37 (n=23)	P value
E ₂ (pg/ml)	1741.5±913.1	2144.7±1163.2	0.277
Number of oocytes retrieved	4.7±4.9	10.2±6.6	<0.01

Table5. Comparison of the culture results in the group below 0.37 and above 0.37.

	Group below 0.37 (n=14)	Group above 0.37 (n=23)	P value
Fertilization rate (%)	86.2	85	0.379
Cleavage rate (%)	100	98.1	0.169
Good blastocyst rate (%)	53	48.9	0.769

There were no significant differences in the E₂ levels among the both groups. However, the number of oocytes retrieved was significantly fewer in the group below 0.37 than in the group above 0.37 (Table4). There was no significant difference in culture results among the both groups.

CONCLUSIONS

It was suggested that the oral GnRH antagonist relugolix used during ovarian stimulation did not affect embryo developmental potential. On the other hand, it was suggested that the lower P₄ level of 2 days before oocyte retrieval in relugolix cycle may result in the fewer number of oocytes retrieved.

IMPACT STATEMENT

It is known that relugolix has a longer blood half-life than that of cetrorelix, therefore we thought that this oral GnRH antagonist is more effective about preventing premature LH surges than cetrorelix. For patients who do not have the expected number of oocytes retrieved, changing the method of relugolix administration (every other day administration or half administration) or changing the trigger may improve the number of oocytes retrieved.