

체외수정시술을 위한 과배란유도에 있어 GnRH Antagonist의 임상적 효용성과 혈중 호르몬 농도의 변화

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Clinical Efficacy and Hormonal Change of GnRH Antagonist in Controlled Ovarian Stimulation for IVF-ET

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Objectives: To evaluate the efficacy of GnRH antagonist cetrorelix in women undergoing controlled ovarian hyperstimulation (COH) for in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) and to determine changes in serum hormone concentrations during cetrorelix administration.

Methods: We performed a clinical trial on 30 patients undergoing COH with highly purified follicular stimulating hormone (HP-FSH) and gonadotropin releasing hormone antagonist (GnRHant), cetrorelix. FSH was administrated from day 2 or 3 of cycle with fixed dose and adjusted according to individual response. 0.25 mg of cetrorelix was injected daily subcutaneously from stimulation day 5 until the day of hCG administration. Daily ultrasound monitoring was performed for growing follicles and serum levels of luteinizing hormone (LH), estradiol (E₂) and progesterone were measured daily during cetrorelix administration. Up to 4 embryos were transferred.

Results: Mean age of enrolled patients was 32.0±3.4 years (mean ± S.D.). All of 30 patients underwent oocyte pick-up, and embryo transfer was done in 28 patients. The total and mean numbers of received oocytes were 196 and 6.5±4.7, the number of fertilized eggs was 111, and the fertilization rate was 56.6%. Total duration of FSH administration was 9.2±2.2 days and mean of 24.3±7.7 ampules of HP-FSH was administered. Total duration of cetrorelix administration was 5.7±1.9 days. Serum LH and progesterone levels were maintained in the range of 1.4~2.9 mIU/mL and 0.3~0.6 ng/mL, which respectively reflected effective prevention of premature LH surge. Clinical pregnancies were achieved in 9 patients, and overall clinical pregnancy rate was 30.0% per oocyte retrieval, and 32.1% per embryo transfer.

Conclusion: GnRH antagonist is safe and convenient for COH for IVF-ET and effective with optimal pregnancy rate.

Key Words: GnRH antagonist, Controlled ovarian hyperstimulation (COH), In vitro fertilization and embryo transfer (IVF-ET)

1978 (gonadotropin-releasing hormone antagonist, GnRHant) (luteinizing hormone, LH) 가 , 3 GnRHant 0.25 mg 가 .⁵⁻⁷ GnRHant GnRH . 1984 Porter GnRHant (gonadotropin-releasing hormone agonist, GnRHa) (follicular stimulating hormone, FSH) LH 가 GnRHa 가 GnRHa 가 LH 가 , 가 GnRHa , GnRHa GnRHant LH, FSH . GnRHa 20% 2% GnRHant 가 .⁸ GnRHant GnRHa .¹² GnRHa LH flare up GnRHant GnRHa . 가 , 가 ,⁹⁻¹¹ GnRHa .³ GnRHa .^{12,13} GnRHant 가 GnRHant 10~14 가 GnRHant 가 GnRHant .⁴

14 mm

5 ,

가 12~14 mm

1. GnRHant (Cetrotide® Serono, Switzerland)

2001 1 2001 11 0.25 mg 18

mm 가 1 FSH

가 19~39 , hCG (Profasi® Serono, Switzerland)

가 24~35 3 10,000 IU

가 3

1 가 1 2) GnRHant가

LH FSH (LH/FSH)가 2 GnRHant가

FSH가

LH, FSH, (estradiol, E₂), (progesterone), (human chorionic gonadotropin, hCG) , GnRHant가

mIU/mL , FSH가 10 LH, E₂, progesterone , hCG

2 cm , FSH 가

3) hCG 10,000 IU 34~36

6 , 8

2. 2 mL Dulbecco's phosphate buffered saline (D-PBS)

1) , 2 ml D-PBS 가

30 , D-PBS

14~17 2 3 가 (oocyte-cumulus cell complex, OCCC)

2 cm

(Metrodin-HP® 4) ICSI (intracytoplasmic sperm injection)

Serono, Switzerland)

(highly purified FSH, HP-FSH)

GnRHant , 가 12~ 6~24 ,

4~6 37 , 5% CO₂ oil (microdroplet) 10%

가 polyvinylpyrrolidone (PVP) 10%

가 1~2×10⁵/mL (midpiece) 가

2 (immobilization)

mL 1~2 37 , 5% CO₂ 1 가

6 , 12 3 9

0.1% hyaluronidase가 가

D-PBS 30 Pasteur pipette

Pasteur pipette (oolemma) 가

3 PVP 가

1

(first polar body)가 2 oil

(Metaphase II) 2 mL 20 μl 1

37 , 5% CO₂ ICSI 3~5 5) 8

ICSI 1 (Metaphase I) 가 (embryo)

1 가 2 grading) 가

ICSI 2% (de- 4

ICSI 30 2 , 100 dry-oven 4

(holding pipette) puller 4

가 microforge progesterone in oil 50 mg (Progest®)

(fire polishing) 15~20 Samil Pharm, Korea)

μm, 100~120 μm (injection pipette) in- 6)

tracytoplasmic micro-pipette 10~12

microforge 30~40° hCG 가 10 mIU/mL 3~4

ICSI 1 (micromanipulator)

3 (tool holder)

(testicular sperm extraction, TESE) 2
(Table 1, 2).

FSH 9.2±2.2 (7~17) ,
FSH ampule 24.3±7.7 (14~55)
GnRHant가 5.7±1.9 (4~13)
estradiol 32.4±12.4 pg/mL
GnRHant가 304.2±200.1
pg/mL, hCG가 1,112.9±961.7
pg/mL .
GnRHant가 LH
1.4~3.4 mIU/mL , LH
가 4.5±1.4 mIU/mL
progesterone
GnRHant 0.3~0.6 ng/mL

LH surge (Table 3, Fi-
gure 1).

30
, 2
, 24
6.5±4.7 (1~23) , 30
가 가 , 2
, 1
1 ICSI

Table 1. Clinical characteristics of 30 patients treated with GnRH antagonist

No. of patients	30
Mean age (yr)	32.0±3.4*
Mean body mass index (kg/m ²)	20.7±2.4*
No. of cycles	1.6±0.9*
ICSI [§]	16/30 (53.3%)
Ejaculated sperm	13
MESA [†]	1
TESE [‡]	2

*Expressed as mean ± standard deviation
[§]Intracytoplasmic sperm injection
[†]Microsurgical epididymal sperm aspiration
[‡]Testicular sperm extraction

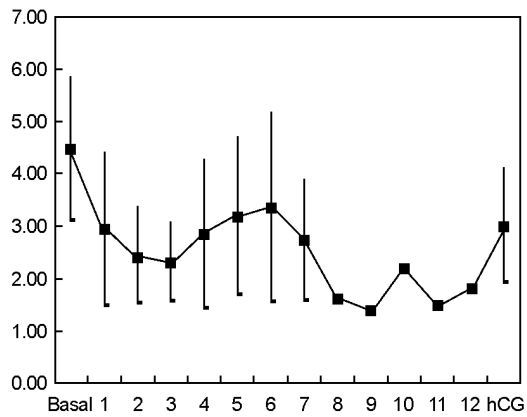
Table 2. Infertility factors of study subjects

Infertility factors	No. of cases (%)
Male factor	8 (26.7%)
Female factor	14 (46.7%)
Endometriosis	2 (6.7%)
Tubal factor	9 (30.0%)
Uterine factor	3 (10.0%)
Both male & female factor	7 (23.3%)
Unexplained	1 (3.3%)

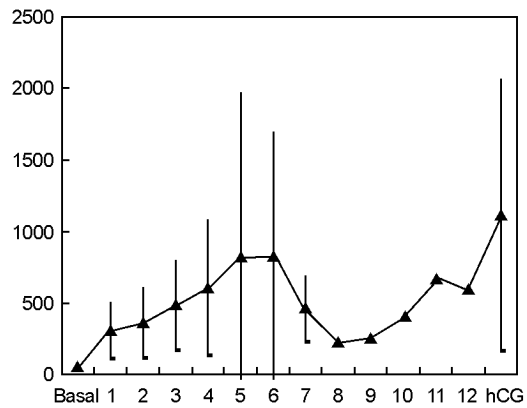
Table 3. Changes in serum hormone concentration

Hormone	Mean
Basal serum FSH (mIU/mL)	6.8±1.9*
Gonadotropin (HP-FSH)	
administration (days)	9.2±2.2*
doses (ampules)	24.3±7.7*
GnRH antagonist (cetrotrelix)	
administration (days)	5.7±1.9*
doses (mg/day)	0.25
Estradiol (pg/mL)	
basal	32.4±12.4*
GnRHant day	304.2±200.1*
hCG day	1,112.9±961.7*

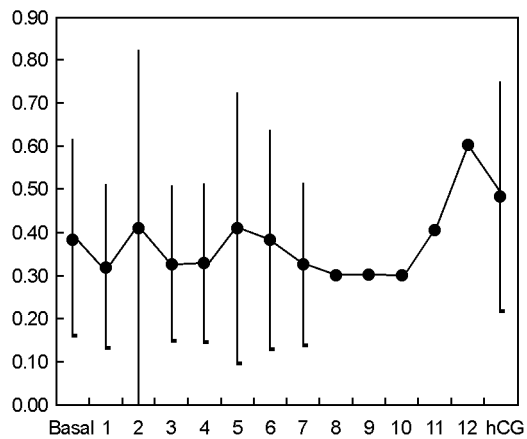
*Expressed as mean ± standard deviation



1-1. Serum LH (mIU/mL)



1-2. Serum estradiol (E₂) (pg/mL)



1-3. Serum progesterone (ng/mL)

Figure 1. Changes in serum hormone levels during GnRH antagonist administration.
Basal: basal serum level
hCG: serum level on hCG administration day

Table 4. Outcomes of in vitro fertilization and embryo transfer

Parameter	Mean
Retrieved oocytes	6.5 ± 4.7*
Fertilization rate	111/196 (56.6%)
Transferred embryos	2.9 ± 1.3*
CES [§]	43.2 ± 28.5*
Clinical pregnancy	
per ovum pick-up	9/30 (30.0%)
per embryo transfer	9/28 (32.1%)

*Expressed as mean ± standard deviation

[§]Cumulative embryo score

196
111 56.6%
2.9 ± 1.3
(1~4) 11 hCG
, 9
32.1%,
30.0% (Table 4).
30 1
(ovarian hyperstimulation syndrome, OHSS)가

1971 Schally
GnRH decapeptide 가
GnRH agonist (GnRHa)
가 .¹⁸ GnRHa
GnRH
GnRHa
down-regulation
LH surge가
GnRH

antagonist (GnRHant)

6.5 가 가

, 2 GnRHant cetorelix 3

GnRHant 가

가 5,6,19,20 GnRH 가 3 7 ICSI

, 7 1 GnRH 6 2

GnRHa GnRHant dose- finding study (Lubeck protocol) 0.25 mg/ brum GnRHant Felber- (French protocol) 3 mg hCG 가 day, 7,19 Albino 가

cetorelix LH 가 LH surge hCG 가 2,111±935 pg/mL 23 0.25 mg 가 1998 ganirelix dose-finding study group , 0.25 mg antagonist가 가

Premature LH surge LH 가 10 mIU/mL 가 1 ng/mL premature luteinization antagonist가 GnRHant가 24 LH, GnRHant가 GnRH LH 가 GnRHant GnRHant가 GnRHant가

가 GnRHant LH long loop, short loop feed-back Ludwig GnRH-

30

ant meta-analysis GnRHa cetorelix
 Grade III
 1993 antagonist
 가
 가 GnRHant
 GnRHa
 가
 antagonist
 가
 GnRHant

26
 27,28
 29~31

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