

체외수정기술시 난포자극호르몬 수용체 유전자 다형성이 과배란유도 및 임신 결과에 미치는 영향

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The Effect of Follicle-Stimulating Hormone Receptor (FSHR) Polymorphism on Outcomes of Controlled Ovarian Hyperstimulation (COH) and In-vitro Fertilization and Embryo Transfer (IVF-ET)

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Objective: To investigate the association of FSH receptor (FSHR) polymorphism at position 680 with outcomes of controlled ovarian hyper-stimulation for IVF-ET in Korean women.

Design: Genetic polymorphism analysis.

Materials and Methods: The FSHR polymorphism was analyzed by PCR-RFLP in 172 ovulatory women below the age of 40 year. Patients with polycystic ovary syndrome, endometriosis, or previous history of ovarian surgery were excluded.

Results: Genotype distribution was 41.9% for the Asn/Asn, 47.7% for the Asn/Ser, and 10.5% for the Ser/Ser FSHR genotype group. There was no difference in age of subjects and infertility diagnosis between genotype groups. When the patients were grouped according to their FSHR genotype, the basal levels of FSH (day 3) were significantly different among the three groups (6.0 ± 0.3 IU/L (mean \pm SEM), 5.8 ± 0.3 IU/L, and 8.6 ± 1.2 IU/L for the Asn/Asn, Asn/Ser, and Ser/Ser groups, respectively, $p=0.002$). The Ser/Ser group showed a higher total doses of gonadotropins required to achieve ovulation induction, and a lower serum estradiol levels at the time of hCG administration compared with other two groups, but the differences were of no statistical significance. The numbers of oocytes retrieved were significantly different among the three groups (8.6 ± 0.8 , 9.9 ± 0.6 , and 6.3 ± 0.9 , for the Asn/Asn, Asn/Ser, and Ser/Ser groups, respectively, $p=0.049$). Clinical pregnancy rates were 42.4%, 25.9%, and

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29.4% for the Asn/Asn, Asn/Ser, and Ser/Ser groups, respectively.

Conclusion: Homozygous Ser/Ser genotype of FSHR polymorphism at position 680 was associated with decreased ovarian response to gonadotropin stimulation for IVF-ET.

Key Words: FSH receptor, Polymorphism, IVF-ET, Controlled ovarian hyperstimulation (COH)

가
가
1
2
가
가
가
가
reserve
가
4
5
aromatase
isoform
inhibitor
isoform
6-8
가
isoform
9,10
chromosome
2p21 to 16
receptor
cyclic AMP
7
transmembrane domain
11
가
307
alanine (Ala)
680
intra-
cellular domain
asparagine (Asn)
serine (Ser)
가
exon 10
가
allelic variant,
Thr307/Asn680
Ala307/Ser680

12,13
680 estradiol 가 300 pg/ml
hCG 10,000 IU
hCG 10,000 IU 36
14
D-PBS YS media
가 가
가 가
2~5
hCG 14 β-
3 mIU/ml , 1
β-hCG
5~6
1.
2002 6 2003 9 3
172 가
75 , 97 14
가 40 7~10 GnRH agonist
14
2.
1)
, 117 3
(68.0%), 43 (25.0%), 12 (7.0%) 2
3 GnRH agonist
, 3
. hCG
14 mm GnRH anta go-
nist 2)
18 mm (1) (PCR)
가 3 , 16 mm 10 mm Wizard DNA

extraction kit (Promega) genomic DNA band as-
 PCR 0.1 µg genomic DNA, paragine homozygote (Asn/Asn), band
 primer 0.4 µM, *Taq* polymerase 1.25 unit, 1.5 mM serine homozygote (Ser/Ser), band
 MgCl₂, 200 µM dNTP band가 hetero-
 PCR primer upstream 5' TTT- zygote (Asn/Ser)
 GTGGTCATCTGTGGCTGC 3', downstream 5'
 CAAAGGCAAGGACTGAATTATCATT 3'
 PCR 94 5 denaturation ,
 94 40 , 58 1 , 72 1 35 (ANOVA), chi-square test
 cycle , 72 10 extension . , SPSS 10.0.7 package . p<0.05

(2) RFLP
 PCR products *BsrI* (New England Biolabs,
 USA)
 10 µl 3% agarose gel 100 voltage
 , 0.5 µg/ml ethidium bro- 680
 mide UV illumination Asn/Asn 41.9% (n=72),
 Asn/Ser 47.7% (n=82), Ser/Ser 10.5%
 (n=18) (Table 1).
 (3)
BsrI 가 asparagine , 가 , 가 ,
BsrI 가 serine 가 ,

Table 1. Distribution of FSHR genotypes by the infertility factors

	Asn/Asn	Asn/Ser	Ser/Ser	Total
Tubal factors	26 (44.1%)	25 (42.4%)	8 (13.1%)	59
Male factors	20 (40.8%)	27 (55.1%)	2 (4.1%)	49
Tubal & Male factors	3 (33.3%)	5 (55.6%)	1 (11.1%)	9
Unexplained	23 (41.8%)	25 (45.5%)	7 (12.7%)	55
All patients	72 (41.9%)	82 (47.7%)	18 (10.5%)	172

Table 2. Age of the patients and applied controlled ovarian hyperstimulation (COH) protocols according to FSHR genotypes

	Asn/Asn	Asn/Ser	Ser/Ser	Total	P value
Age	32.4±0.4*	33.1±0.4	33.6±0.7	32.9±0.3	0.167
COH Protocol					
Antagonist protocol	50 (42.7%)	55 (47.0%)	12 (10.3%)	117	
Long protocol	15 (34.9%)	24 (55.8%)	4 (9.3%)	43	
Short protocol	7 (58.3%)	3 (25.0%)	2 (16.7%)	12	
All patients	72 (41.9%)	82 (47.7%)	18 (10.5%)	172	

Values are mean ± SEM.

(Table 1).

(Table 2).

3

Asn/Asn 6.0 ± 0.3 (\pm SEM) IU/L, Asn/Ser 5.8 ± 0.3 IU/L, Ser/Ser 8.6 ± 1.2 IU/L Ser/Ser (p=0.002).

Asn/Asn $2,203 \pm 88$ (\pm SEM) IU, Asn/Ser $2,255 \pm 80$ IU, Ser/Ser $2,554 \pm 264$ IU, Ser/Ser (p=0.237) (Table 4).

hCG estradiol Asn/Asn 가 single nucleotide polymorphism (SNPs) 가

$1,640 \pm 140$ (\pm SEM) pg/ml, Asn/Ser $1,767 \pm 124$ pg/ml, Ser/Ser $1,185 \pm 189$ pg/ml, Ser/Ser (p=0.167) (Table 4).

Asn/Asn 8.6 ± 0.8 , Asn/Asn

Table 3. Basal FSH levels according to FSHR genotypes

	Asn/Asn	Asn/Ser	Ser/Ser	P value
Mean \pm SEM (IU/L) ^a	6.0 ± 0.3	5.8 ± 0.3	8.6 ± 1.2	0.002
Median (IU/L)	5.6	5.4	7.6	
Range	0.6~16.4	0.3~14.5	2.7~20.6	

Values are mean \pm SEM.

Table 4. Outcomes of controlled ovarian hyperstimulation according to FSHR genotypes

	Asn/Asn	Asn/Ser	Ser/Ser	P value
Dosage of gonadotropin used (IU)	$2,203 \pm 88$	$2,255 \pm 80$	$2,554 \pm 264$	0.237
Peak estradiol (pg/ml)	$1,640 \pm 140$	$1,767 \pm 124$	$1,185 \pm 189$	0.167
No. of oocytes retrieved	8.6 ± 0.8	9.9 ± 0.6	6.3 ± 0.9	0.049
Clinical pregnancy rate*	42.4%	25.9%	29.4%	0.101
		26.5%		0.034

Values are mean \pm SEM. *, per transfer

680

161 Ser/Ser 가 Mayorga (2000)

Asn/ Ser/Ser 29% (n=46), Asn/Ser 45% (n=72), Ser/Ser 26% (n=43) 가

hCG estradiol

40.7±2.3 , 46.8±5.0 31.8±2.4 ,

(p<0.01). 6.4±0.4

IU/L, 7.9±0.3 IU/L, 8.3±0.6 IU/L 가

(p<0.01).

가 가 가

680 Mayorga (2000)

가

가

down regulation

16

680 asparagine glycosyla- tion

, serine phosphorylation

가 17

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