

Investigating the association between polymorphism of follicle-stimulating hormone receptor gene and ovarian response in controlled ovarian hyperstimulation

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ABSTRACT

AIM: The aim of the study was to investigate the association between follicle-stimulating hormone receptor (FSHR) gene polymorphism at Position 680 and the outcomes of controlled ovarian hyperstimulation for *in vitro* fertilization and embryo transfer (IVF-ET) in infertile women. **MATERIALS AND METHODS:** One hundred and eight patients under 35 years of age who underwent IVF-ET procedures were included in this study. The hormonal profile and treatment of all patients were analyzed and FSHR polymorphism was examined by polymerase chain reaction-restriction fragment length polymorphism. Women from all groups were classified based on polymorphisms at Position 680, occupied either by asparagines (Asn) or serine (Ser) as Asn/Asn, Asn/Ser, and Ser/Ser genotype. **RESULT:** Our study showed that all patients in the Asn/Asn group were normal responders and in the Asn/Ser group 64.8% were normal responders and 21.1% and 14.1% were poor and hyper responders respectively. In the Ser/Ser group we did not have normal responders and 46.7% of these patients were poor responders and 53.3% were hyper responders. **CONCLUSION:** FSH receptor polymorphism is correlated with response to ovarian stimulation.

KEY WORDS: Follicle-stimulating hormone receptor, ovarian response, ovarian stimulation, polymorphisms

INTRODUCTION

Follicle stimulating hormone (FSH) and luteinizing hormone (LH) are two pituitary glycoproteins which are essential for normal gonadal function. They coordinate and regulate gonadal growth, differentiation, endocrine function and gametogenesis in both sexes.^[1,2] The interaction of FSH hormone with its cell surface receptor initiates a chain of intracellular reactions characteristic of G protein-coupled receptors. These include stimulation of adenylate cyclase and phosphorylation of specific proteins.^[3,4] The FSH receptor is composed of a large N-terminal extracellular domain and seven-transmembrane domains. The latter include three outside and inside loops connecting them, together with an intracellular C-terminal tail. The ligand-binding, large

N-terminal extracellular domain is unique to FSH, the LH/chorionic gonadotrophins and thyroid-stimulating hormone receptor. All belong to the same subfamily of G-protein-coupled seven-transmembrane receptors. The C-terminal tail of the FSH receptor, located in the cytoplasm, contains a high proportion of serine threonine residues, which might be potential substrates for receptor phosphorylation.^[5,6] During screening for mutations of the follicle-stimulating hormone receptor (FSHR) gene, two polymorphisms were identified: One located in the extracellular domain at Position 307, occupied by either alanine (Ala) or threonine (Thr); and the other one, located in the intracellular domain at Position 680, occupied either by asparagines (Asn) or serine (Ser). Both polymorphic sites are within Exon 10 and give rise to two discrete

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allelic variants of the FSHR, i.e. Thr307/Asn680 and Ala307/Ser680. While some researchers reported that there was no difference regarding frequencies of these polymorphisms between infertile couples and normal population,^[7-9] some others found differences in the genotype distribution between the control group and the anovulatory infertile group or polycystic ovary syndrome (PCOS) woman population.^[10,11] In addition, an Ala189Val mutation of FSHR has been reported to be related to hypergonadotropic ovarian failure.^[12]

Recently, a hormone-specific beta subunit of FSHR was evaluated for polymorphism, and the sequence analysis shows that this gene is highly conserved and its polymorphisms are apparently extremely rare.^[13]

In assisted reproduction programs, the response of ovulating women to exogenous FSH therapy is quite variable. Despite several years of clinical experience, the prediction of ovarian response to intense gonadotrophin stimulation is difficult. Patient characteristics, rather than the stimulation protocol, seem to determine the individual response. In young ovulating women undergoing *in vitro* fertilization (IVF) treatment, the standard stimulation protocol can result in either poor response (requiring adjustment of the FSH doses) or in ovarian hyperstimulation syndrome (OHSS). This is a serious, potentially life-threatening complication of IVF characterized by enlarged ovaries and extravasations of fluid to the abdominal cavity, resulting in ascites, hypovolemia, and hemoconcentration. OHSS is typically iatrogenic following gonadotrophin administration. The genetic studies have addressed the issue that the mutations in the FSHR could be activating, leading to a predisposition to OHSS. In addition, it was reported that Ser680Asn genotype, in the FSHR gene is a predictor of the severity of symptoms in patients who develop OHSS.^[14] Advance identification of patients who will elicit a poor response or hyper response to standard treatment would be of great clinical advantage for such patients. Moreover, a few mutations of the FSHR gene were recently found and described a molecular basis for the pathogenesis of OHSS.^[15] It is believed that patients should be counseled about this iatrogenic complication before starting ovarian stimulation procedures.^[16] However, polymorphisms of the FSHR have been associated with the response to FSH in controlled ovarian hyperstimulation (COH), as well as with the severity of OHSS when present.^[17] Several parameters have been postulated as predictors of the ovarian response. Of these, FSH seems to have the best predictive value, but the significant intra-individual variability from cycle to cycle has to be taken into consideration.^[18] Other factors proposed to affect ovarian response to FSH are the distribution of FSH isoforms and the interference of circulating FSH binding inhibitors or FSH antibodies. Intra-ovarian interference,

at the level of the FSH binding to its cognate receptor, and the presence of FSHR isoforms with altered signal transduction have also been discussed.^[19] However, none of these hypotheses have been proven up to now. In this paper, we demonstrate the relation between FSHR genotype and ovarian responsiveness to FSH in ovulation induction.

MATERIALS AND METHODS

108 women who were referred to a tertiary centre for infertility and underwent an IVF-ET procedure were recruited for this study. All women were younger than 35 years of age and underwent the procedure in response to tubal, male or ovarian factor infertility. Patients with endometriosis or previous history of ovarian surgery were excluded from this study. All the patients had history of infertility for at least one year. The study protocol was approved by the ethics committee and each patient received full description of the purpose this study. Basal FSH levels (Day 3 of menstrual cycle) were obtained in one of the previous cycles before ovarian stimulation. In all cases, controlled ovarian stimulation was performed. Highly purified FSH (Metrodin-HP, Serono, Switzerland) or recombinant FSH (Gonal-F, Serono, Switzerland) was used for COH. For gonadotrophin releasing hormone (GnRH) agonist long protocols, daily treatment with 0.5 mg Suprefact (Suprefact, Aventis Pharma, Germany) began on Day 21 of the cycle preceding the stimulation cycle, and continued until onset of menstruation, at that time the dosage was decreased to 0.25 mg daily, this continued until the day of the human chorionic gonadotrophin (hCG) treatment. Treatment with 2 to 4 ampoules of FSH, depending on the patient's previous or anticipated responses was initiated on Day 2 of the menstrual cycle. In women with no previous attempt, the criteria used to determine the initial dose of FSH were age and body mass index (BMI). Higher dose was applied to older patients and women with more BMI. Treatment was then individualized in a step-down fashion. When the leading follicle reached 18 mm in mean diameter, 10000 unit of hCG (Profasi, Serono, Switzerland) was administered. Oocyte retrieval was performed 36 h after the hCG injection. The intracytoplasmic sperm injection (ICSI) was performed according to conventional protocols and on the metaphase II oocytes. Up to three embryos was transferred on the second or third day after retrieval. The patients were individualized to three groups according to numbers of mature follicles (more than 14 mm in diameter) on the day of the hCG injection. Patients with three or less mature follicles were considered poor responders. Those with three to 15 mature follicles were considered as normal and those with more than 15 mature follicles were considered as high responders. In this latest group, to prevent OHSS, the following actions were performed. First the gonadotrophins were withheld

for one to two days to bring the serum estradiol level under 3000 pg/ml. The second step was prescription of Cabergoline 0.5 mg/day orally for eight days, starting from the day of hCG injection. Finally, after egg retrieval and performing IVF, the embryos were frozen by vitrification method and the transfer was postponed for at least two cycles. By doing these actions, none of the patients in the high responders group developed OHSS. Analysis of FSHR gene polymorphism was performed from 10 ml peripheral venous blood sample with Ethylenediaminetetraacetic acid (EDTA). Genomic DNA was extracted from peripheral blood using phenol/chloroform method. The FSHR polymorphism at Position 680 was determined by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) analysis. PCR reaction mixture contained 0.1 µg of genomic DNA, 0.4 µM of each primer: (upstream 5' TTTGTGGTCATCTGTGGCTGC3', downstream 5' CAAAGGCAAGGACTGAATTATCATT3'), 1.25u of Taq polymerase, 1.5 mm of MgCl₂, and 200 µm of dNTP. Following an initial denaturation step at 94°C for 5 min, samples were subjected to 30 rounds of PCR. Products were digested with 2 IU of restriction enzyme BsrI (New England Biolabs, USA) followed by electrophoresis on 2% agarose gel, and the digested products were identified using ethidium bromide staining. Uncleaved band indicated the asparagines homozygote (Asn/Asn), cleaved bands the serine homozygote (Ser/Ser), and simultaneous cleaved and uncleaved bands the heterozygote (Asn/Ser).

Statistical analysis

The data were analyzed with SPSS 13.0. Data were analyzed using the Chi-square test or the exact Fisher when it was necessary. *P* value <0.050 was considered statistically significant.

RESULTS

One hundred and eight patients were included in this study. They were classified into three groups according to FSHR genotype at Position 680; Asn/Asn, Ser/Ser and Asn/Ser. In total, the results indicated that 22 patients had Asn/Asn genotype (20.37%), 71 showed Asn/Ser genotype (65.74%) and in 15 patients Ser/Ser genotype was detected (13.89%). The mean age of the three genotype groups was similar. Infertility factor were classified as male factor (*n* = 60), tubal factor (*n* = 10), ovarian factor (*n* = 19) and unexplained (*n* = 19). The distribution of these infertility factors is shown in Table 1, with no significant difference (*P* > 0.050). The mean of Day 3 basal FSH levels was similar in all three groups; Ser/Ser 5.7 ± 2.1 IU/L, Asn/Ser 6.9 ± 3.7 IU/L and Asn/Asn 5.9 ± 2.9 IU/L (*P* value = 0.643). The dosage of gonadotrophins used and serum estradiol levels on the day of the hCG administration were not significantly different among the three genotypes as is mentioned in Table 2. The number of

Table 1: Age of patients and distribution of FSHR genotype by infertility factors

Variable	Asn/Asn	Asn/Ser	Ser/Ser	<i>P</i> value
Female age (years)*	30 ± 4.1	30.1 ± 4.3	28.8 ± 5.7	0.590 ^a
Male factor no.	13 (59.1)	37 (52.1)	10 (66.7)	0.387 ^b
Tubal factor no.	1 (4.5)	7 (9.9)	2 (13.3)	0.174 ^b
Ovarian factor no.	3 (13.6)	14 (19.7)	2 (13.3)	0.401 ^b
Unexplained no.	5 (22.7)	13 (18.3)	1 (6.7)	0.105 ^b
Total no.	22 (100)	71 (100)	15 (100)	

*Data are presented as mean±SD; ^aUsing *t*-test; ^bUsing Chi-square test; FSHR - Follicle-stimulating hormone receptor; Asn - Asparagines; Ser - Serine, Figures in parenthesis are in percentage

Table 2: Outcomes of controlled ovarian hyperstimulation according to FSHR genotypes

	Asn/Asn (<i>n</i> = 22)	Asn/Ser (<i>n</i> = 71)	Ser/Ser (<i>n</i> = 15)	<i>P</i> value
Dosage of gonadotrophins (IU)*	1670 ± 65	1725 ± 60	1500 ± 150	0.501 ^a
Peak estradiol (pg/ml)*	1650 ± 132	1506 ± 120	1200 ± 167	0.212 ^a
No. of mature follicles*	12.36 ± 5.1	11.86 ± 9.3	13.6 ± 11.9	0.792 ^b
No. of oocytes retrieved*	5.91 ± 2.7	4.52 ± 4.3	3.13 ± 4.5	0.022 ^b
Clinical pregnancy rate per transfer	18.2% (<i>n</i> = 4)	11.3% (<i>n</i> = 8)	13.33% (<i>n</i> = 2)	0.395 ^b

*Data are presented as mean±SD; ^aUsing student *t*-test; ^bUsing Chi-square test; FSH - Follicle stimulating hormone, Asn - Asparagines, Ser - Serine

mature follicles on the day of the hCG injection was similar in all three groups while the number of oocytes retrieved in the Asn/Asn group was more than in the other groups and the difference was statistically significant (*P* value = 0.022). In addition, the clinical pregnancy rates per embryo transfer in the Asn/Asn group were more than the other groups but the difference was not statistically significant [Table 2]. In this study the patients were individualized to three groups according to the number of mature follicles on the day of the hCG injection; poor responders, normo responders and high responders. In total, 22 patients were poor responders, 68 were normal responders and 18 were hyper responders. None of these 18 hyper responder patients presented an OHSS because of the preventive actions. In the Asn/Asn group all our patients were normal responders but in the Asn/Ser group we had 21.1% poor responders, 64.8% normal responders and 14.1% hyper responders. In the Ser/Ser group we did not have any normal responders, while 46.7% of patients were poor responders and 53.3% of patients were hyper responders [Table 3].

DISCUSSION

FSH is essential for normal reproductive function. Due to the important roles of FSH in follicular growth and ovarian steroidogenesis in females and spermatogenesis in males, mutations in FSH receptor gene could affect reproductive

Table 3: Ovarian response to ovarian hyperstimulation according to the three FSHR genotypes

Variable	Asn/Asn (n = 22)	Asn/Ser (n = 71)	Ser/Ser (n = 15)	P value
Poor responder	0	15 (21.1)	7 (46.7)	0.008 ^a
Normal responder	22 (100)	46 (64.8)	0	0.004 ^a
Hyper responder	0	10 (14.1)	8 (53.3)	0.037 ^a

^aUsing Chi-square test, FSHR - Follicle-stimulating hormone receptor; Asn - Asparagines, Ser - Serine; Figures in parenthesis are in percentage

ability, especially in women.^[20] FSH is crucial for oocyte maturation. It was shown that the granulosa cells, which express the FSH receptor, interact with the oocyte, and control the oocyte maturation.^[21]

Since the human genome was mapped much progress has been made in the search for genes related to ovarian function.^[22] The genotypic variance of the FSHR was reported for the first time by Aittomaki *et al.*, in 1995.^[23] After that time the possibility has been considered as to whether a signal nucleotide polymorphism of FSHR gene affects the ovarian response to exogenous gonadotrophins or not. It could suggest that the ovarian responses to gonadotrophins for COH in IVF-ET cycles might differ according to the FSHR gene genotypes. Perez Mayoral *et al.*, evaluated the impact of FSHR genotypes at Position 680 on the ovarian responses to FSH stimulation in 161 infertile women undergoing IVF-ET. Although no differences were observed in terms of the number of oocytes retrieved and serum estradiol concentration on the day of the hCG injection, the number of gonadotrophin ampoules and basal FSH levels were found to be higher in the Ser/Ser group. It was concluded that FSHR gene genotype is an important factor for determining the prognosis of COH cycles of normo ovulatory infertile women.^[19] Jun *et al.*, investigated the association between FSH receptor polymorphism at Position 680 and the outcomes of COH. They showed that the Ser/Ser group required a higher dose of gonadotrophins for COH and tended to show lower serum estradiol at the time of hCG administration. In addition, the Asn/Asn group tended to have higher oocyte retrieval and had higher pregnancy rate compared to other groups.^[24] Similarly, Sudo *et al.*, showed the same results.^[20] A retrospective study in IVF patients has shown an association between the presence of Serin in Position 680 and poor responses to gonadotrophins.^[25] Later, Perez Mayorga *et al.*, showed that genotype in Position 680 of FSH is a predictor of severity in OHSS patients.^[19] In another study, Daelemans *et al.* reported that the OHSS population had an even higher enrichment in the S680 allele compared with the Caucasian control population.^[26] Interestingly and in agreement with these studies, our study showed that in the Ser/Ser group there was no normal responder while 46.7% of these patients were poor responders and 53.3% were hyper responders. None of the hyper responder patients in our study developed OHSS due to the preventive actions

performed by our specialists. But we can compare them with the OHSS patients in other studies, as both have high response to COH. Therefore, it is very important to identify the patients at the risk of developing OHSS before the start of the IVF protocol, and studying different gene polymorphisms in this regards can be very helpful. Our study and other similar studies can finally lead to the situation where specific criteria for choosing the proper protocol for COH is available.

Lourtradis *et al.*, reported that good responders are more often the Asn/Ser type and in addition, the Ser/Ser variant might be related to higher serum FSH levels, while the Asn/Ser is related to lower FSH levels.^[27] However, the present study showed that regarding different FSHR genotypes, there were no significant differences in the dosage of gonadotrophins used, peak estradiol level and clinical pregnancy rate in the women who underwent the IVF-ET procedure in a tertiary Clinical and Research Center for Infertility. While there was a significant difference in the number of oocytes retrieved and the response to ovarian stimulation among different genotypical groups. All the patients in the Asn/Asn group were normal responders, while in the Asn/Ser group, 64.8% were normal responders and 21.1% and 14.1% were poor responders and hyper responders respectively.

Overall, most studies showed the effects of FSHR gene polymorphism on the results and complication of assisted reproductive technology (ART) and not on infertility. We performed this study on infertile patients and found a rate of 20.37% for the Asn/Asn genotype, 65.74% for the Asn/Ser genotype and 13.89% for the Ser/Ser genotype which were similar to the rates found in the other studies on different groups of patients and normal individuals. For example, in a study by Binder *et al.*, in ART patients with or without OHSS and in normal fertile women the rate of the Asn/Asn, Asn/Ser and Ser/Ser genotypes was 15.4%, 51.6% and 33.0% respectively in the OHSS group. These rates were 17.4%, 46.5% and 36.1% respectively in the 'ART/no OHSS' control group and 24.8%, 54.6% and 20.6% respectively in the normal fertile group.^[28] In another study by Livshyts *et al.*, on patients with ovarian dysfunction and on normal fertile women who gave birth to naturally conceived children, under 35 years of age, the rates of the Asn/Asn, Asn/Ser and Ser/Ser genotypes were 18.6%, 53.9% and 27.5% respectively in patients with ovarian dysfunction and 33.1%, 52.3% and 14.6% respectively in the normal fertile group.^[29]

In conclusion, this investigation reveals that in a population of infertile women, FSH receptor gene polymorphism at Position 680 is associated with a different ovarian response to COH. Different studies investigated the pathophysiological role of FSH receptor polymorphisms in ovarian dysfunction or ovarian response to stimulation, but there is still some uncertainty about this, and doing more researches in this regard, as we have tried, can solve this uncertainty. As

Livshyts *et al.*, mentioned, further studies can clarify the role of each polymorphism in FSHR protein bioactivity.^[29]

Finally, we should consider that there are investigators like Klinkert *et al.*, (2006) who found the ovarian response comparable between the three genotypes, while patients with the Ser/Ser genotype had implantation and pregnancy rates three times higher as compared with patients with the Asn/Asn polymorphism.^[30] Thus, it should be noted that there is a great heterogeneity in the results that concern the efficacy of this genetic marker for the prediction of the ovarian response and pregnancy outcome. Therefore, these findings should be confirmed in larger studies, which will probably reveal more significant results. In addition, further studies are necessary to determine whether it is possible to apply this relationship to the pre-cycle evaluation of individual genetic predisposition in terms of preventing either OHSS or low ovarian response.

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