Effect of follicle-stimulating hormone receptor N680S polymorphism on the efficacy of follicle-stimulating hormone stimulation on donor ovarian response

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Objective **The aim of this study was to investigate whether N680S FSHR polymorphism has a predictive value for the ovarian response to stimulation with gonadotropins and cycle outcome in our egg donor program.**

Methods **The oocyte donor candidates were selected according to the Instituto Bernabeu egg donation program requirements and ASRM and ESHRE guidelines for oocyte donation. The FSHR polymorphism N680S was studied in 145 oocyte donors. All donors underwent controlled ovarian hyperstimulation (COH) ($n=355$) using urinary follicle-stimulating hormone in a GnRH antagonist protocol and receiving a GnRH agonist triggering. The main outcome measures were oocyte yield, days of stimulation, gonadotropin doses, biochemical pregnancy, ongoing pregnancy, and miscarriage rates.**

Results **Significant differences were reported in the antral follicle count (16.5±5.0 for NN, 14.5±4.7 for NS, and 14.1±3.8 for SS), number of eggs retrieved (21.5±9.2 for NN, 18.5±8.2 for NS, and 19.8±8.9 for SS), and gonadotropin doses (2098.5±639.4 IU for NN, 2023 ±490.1 IU for NS, and 2149.5±552.3 IU for SS) between the genotypes. The clinical outcome was not affected by the N680S polymorphism of the *FSHR* gene in the egg donors.**

Conclusion **In a population of fertile egg donors, the *FSHR* gene polymorphism at position 680 is associated with different ovarian responses to COH. The genotype of the *FSHR* gene is an important factor for determining the prognosis of the COH cycles in normo-ovulatory fertile women.** ***Pharmacogenetics and Genomics*** **00:000–000** © **2013 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

It is well recognized that an individual variability in response to drugs exists [1]. Although many nongenetic factors influence the effects of medications, during recent years, it has become evident that genetic factors could explain the differences between individuals in terms of drug response. These differences are due to sequence variants in the genes encoding drug targets [2].

More than 19 million single-nucleotide polymorphisms (SNPs) have been identified within the human genome [3]. Some of these SNPs have already been associated with changes in the effects of drugs. The challenge for pharmacogenetics is to establish the relation between the gene variant and the medication response and to develop diagnostic tests that can predict drug action and modify therapy accordingly [2].

Follicle-stimulating hormone (FSH) is a key factor in human reproduction. FSH and its receptor (FSHR) play a major role in follicular development and regulation of steroidogenesis within the ovary [4]. The *FSHR* gene is localized on chromosome 2p21 and spans a region of 54 kb [5]. It consists of 10 exons [6].

Controlled ovarian hyperstimulation (COH) using FSH alone or in association with luteinizing hormone, in different regimens, is a widely used strategy in assisted reproductive techniques (ART). The ovarian response to FSH, however, varies widely among women undergoing ovarian stimulation [7]. Approximately 9–24% of women undergoing IVF respond more poorly than expected to the ovarian stimulation protocol prescribed in accordance with their clinical characteristics [7]. Prior identification of patients who will elicit a poor response to standard treatment would be of great clinical advantage for such patients. Various predictive markers of COH outcome have been proposed, such as age [8], ovarian reserve [9], hormonal status [10], and cigarette smoking [11]. Besides these parameters, genetic variability also seems to be an important factor. Application of pharmacogenetics to ovarian response may predict stimulation success [12] and may also help to adjust and design the doses before undertaking the treatment.

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Almost 1000 SNPs have been located within the *FSHR* gene, but only a few are located within the exons. Two of these SNPs, located at codon 307 and 680, are related to ovarian response. The first SNP is found within the extracellular domain (codon 307) and the second lies within the intracellular domain (codon 680). Both SNPs affect gene function by changing the properties of the gene product and consequently modifying the response to FSH [13]. Threonine (T) can be substituted by alanine (A) at position 307 and serine (S) can be substituted by asparagine (N) at position 680. These polymorphisms are in linkage disequilibrium, resulting in the most frequent allelic combination of T307-N680 and A307-S680. For the purpose of simplification, most studies focus almost exclusively on polymorphisms at codon 680. Clinical studies have demonstrated that the N680S polymorphism determines ovarian response to FSH stimulation in patients undergoing IVF treatment [14–16]. The amount of FSH needed for COH to achieve similar peak estradiol levels was lower in women with the genotype N/N at position 680, suggesting a lower sensitivity of the S680 allele for FSH and a poor response to gonadotropins [17]. Patients with the S680 allele require more FSH during the stimulation phase. In fact, the S/S genotype leads to higher serum levels of FSH and a prolonged cycle, which suggest a lower sensitivity to exogenous FSH. At the time of human chorionic gonadotropin administration, estradiol levels per oocyte retrieved for IVF in the S/S group were significantly lower as compared with the levels in the N/S and N/N groups. This lower response could be overcome by increasing the dose of FSH [18]. There is an association between the ovarian reserve and response, and this could suggest an important role of the FSHR genotype. However, recent studies have been published reporting that ovarian reserve markers are not associated with the FSHR N680S polymorphism [19,20].

To show a correlation between the N680S FSHR polymorphism and COH, we proposed evaluating the ovarian stimulation in a nonconfounding model such as patients from the egg donation program, because egg donors are young fertile women with normal ovulations, and there is a minimal variability in the oocyte and embryo quality. The goal of this study was to investigate whether the N680S FSHR polymorphisms have a predictive value for the ovarian response to stimulation with FSH, oocyte yield, dose of FSH, days of stimulation, and cycle outcome during an oocyte donor program.

Materials and methods

Study population

Egg donations are the best model to evaluate the determinants of implantation for several reasons. First, oocyte and embryo quality vary minimally as the donors are young women with normal ovulation. Second, the preparation of the endometrium is similar as all recipients receive the same hormone replacement protocol.

The selection and recruitment of donors is carried out at our clinic following strict quality criteria, including an extensive chromosomal and genetic evaluation. All donors must be Mediterranean and must meet the legal requirements in Spain (Spanish Law 14/2006). They must be between 18 and 35 years of age, healthy, and with no family history of hereditary diseases. The donors undergo a complete gynecological examination, karyotyping, and screening for infectious diseases such as HIV, hepatitis B and C, gonoccocia, and syphilis. In addition to the legal requirements, we perform genetic screening for cystic fibrosis, fragile X, and α and β thalassemia. Furthermore, guidelines of both ASRM and ESHRE for oocyte donors are followed.

In this study, we include the results of the FSHR 680 polymorphism in 145 oocyte donors. These donors underwent 355 COH cycles, and the results from stimulation and cycle outcome were included in the present research. The average number of COH cycles per donor was 2.6 ± 2.1.

All women included in the study gave their informed consent to collect peripheral blood samples suitable for molecular analysis. This study involved only a retrospective analysis of the anonymous medical records and was approved by the Instituto Bernabeu Institutional Review Board.

Genotyping

DNA was isolated from peripheral blood lymphocytes according to the manufacturer's instructions (Wizard Genomic DNA Purification Kit; Promega, Madison, Wisconsin, USA) and stored at 4°C. Analysis of the *FSHR* gene polymorphism at position 680 was carried out using predesigned TaqMan allelic discrimination assays (rs 6166; Life Technologies Corporation, Carlsbad, California, USA). Real-time PCR was performed using the StepOne plus system from Applied Biosystems (Carlsbad, California, USA) in accordance with the manufacturer's instructions. The analysis was carried out in accordance with the instructions for the device used.

Ovarian stimulation and oocyte retrieval

After being qualified as fulfilling the Spanish Fertility Act requirements, all the donors were administered a controlled ovarian stimulation protocol with tailored doses of urinary FSH (Fostipur; Angelini International, Barcelona, Spain). Gonadotropin stimulation started from day 2 of their menstrual cycles, with doses varying between 150 and 300 IU/day, depending on the age of the donor, BMI, and antral follicle count (AFC). Cetrorelix (Cetrotide; Merck-Serono, Paris, France), a GnRH antagonist, was administered at a dose of 0.25 mg/day,

according to a multiple dose flexible protocol. In all cases, triggering was exclusively performed with 0.4 mg of subcutaneous triptorelin (Decapeptyl; Ipsen Pharma, Paris, France). The ovarian response was monitored by means of transvaginal ultrasounds and plasma estradiol concentrations. The oocytes were aspirated 36 h after analogue administration using transvaginal ultrasound-guided needle aspiration under sedation. Sperm and oocyte preparation, fertilization, embryo culture, and transfer were performed according to the IVF laboratory guidelines.

Recipient protocol

Recipient women carried out a standard protocol as previously reported [21]. The number of previous IVF cycles with donor eggs per recipient was on average 1.5 ± 0.8. In short, patients with ovarian activity received in the luteal phase of their previous cycle either birth control pills or an analogue depot (Decapeptyl depot 3.75; Ipsen Pharma). In contrast, menopausal patients (67.8% of the study recipient patients) were treated with a sequential regime of estrogen and progesterone (Utrogestan 200 mg; Seid, Paris, France), a month before the real treatment. Oral estradiol valerate (Progynova; Schering, Kenilworth, New Jersey, USA) or estradiol patches releasing 50 μg daily (Dermestril 50; Rottapharm-Madaus, Monza, Italy) were used for increasing the doses for endometrial preparation. Patients received up to 6 mg estradiol valerate per day or three patches every other day, and the duration of the treatment varied in accordance with the availability of a phenotypically matched donor, ranging from 14 to 24 days. After 13 days of E2 valerate administration, the endometrial thickness and pattern were tested. If a trilaminar pattern was observed in an endometrium with a thickness of 7 mm or more, the aforementioned dose of E2 therapy was continued at least until the pregnancy test was performed 2 weeks later. If the endometrium was not seen to be sufficiently developed, the doses of E2 valerate were increased to 8 mg/day or four patches. From the day of oocyte retrieval until the pregnancy test was performed, 600 mg of micronized progesterone (Utrogestan 200 mg; Seid) were administered vaginally daily.

Statistical analysis

Values are presented as averages ± SD and medians and range for continuous data and percentages for categorical variables. Data were analyzed using the statistical package for the social sciences software (version 16.0; SPSS Inc., Chicago, Illinois, USA). The primary endpoints were gonadotropin consumption, stimulation length, and total number of oocytes retrieved from donors. Donor characteristics that were continuous variables were tested using analysis of variance to evaluate the differences among the groups. Pearson's χ^2-test was used for categorical variables. Linear regression was applied for AFC, adjusting for age, previous fertility, and smoking status as the possible confounding factors, as these have been reported to affect the ovarian reserve. Linear regression was applied to evaluate the donor ovarian stimulation parameters, adjusting for age, AFC, previous fertility, and smoking status as the possible confounding factors, as these have been reported to affect the ovarian response. Genotypes were included in the model as dummy variables using the SS genotype as a reference. A P value of less than 0.05 was considered significant.

Results

FSHR N680S polymorphism genotyping

All candidates for the Instituto Bernabeu egg donation program have to pass a psychological evaluation and a gynecological checkup according to the ASRM and ESHRE guidelines for oocyte donors. Thereafter, infectious and genetic studies are carried out to ensure the health of the offspring. Karyotyping, screening for α and β thalassemia, cystic fibrosis, and fragile X genetic screening are part of our strict selection and recruitment protocol and consequently have been performed on all of our egg donor candidates. A total of 145 women were examined for the FSHR variant N680S in this study. In total, the results indicated that 61 donors had the SS genotype (42%), 58 (40%) had the NS genotype, and 26 (18%) had the NN genotype. The genotype frequencies were consistent with the Hardy–Weinberg equilibrium.

Ovarian stimulation

The 145 oocyte donors included in this study underwent 355 COH cycles. Table 1 shows the general and clinical characteristics of the donors; no differences were observed in the donor age (25.3 ± 3.9, 26.1 ± 3.7, and 25.4 ± 3.9 years; $P = 0.144$) and previously proven fertility (91.4, 89.4, and 88.7%; $P = 0.784$) between the SS, NS, and NN genotypes for the FSHR 680 polymorphism, respectively. As regards the smoking status in the NN genotype group, only 46.6% smoke versus 62.1% for the NS and 76.2% for the SS groups, with a statistical significance ($P < 0.001$). Differences in the AFC were reported between the genotypes: 16.5 ± 5.0 for NN, 14.5 ± 4.7 for NS, and 14.1 ± 3.8 for SS ($P = 0.001$). Table 2 summarizes the different groups of ovarian stimulation parameters during the 355 COH cycles. Various predictive markers of COH outcome have been proposed, such as age, ovarian reserve, and cigarette smoking. To avoid confounding effects of these predictive markers, we adjusted the statistical analysis. We report significant differences in the number of eggs retrieved among the genotypes; carriers of the NN genotype retrieved more oocytes (21.5 ± 9.2) compared with the NS (18.5 ± 8.2) and SS (19.8 ± 8.9) ($P < 0.001$) genotype carriers. The gonadotropin doses correlated with the genotype in the FSHR polymorphism; women from the SS group required significantly more gonadotropin (2149.5 ± 552.3 IU) compared with the other groups (2098.5 ± 639.4 IU for NN and 2023.5.7 ± 490.1 IU for NS;

Table 1 Donor baseline characteristics in relation to the *FSHR* S680 genotype

	Total (145)			SS (61)			NS (58)			NN (26)			
FSHR N680S genotype	Average±SD	Median	Range	Average±SD	Median	Range	Average±SD	Median	Range	Average±SD	Median	Range	*P*
Donor age (years)	25.6±3.8	26.0	15	25.3±3.9	26.0	15	26.1±3.7	26.5	15	25.4±3.9	25.0	12	0.144
Proven fertility (%)	90.1	–	–	91.4	–	–	89.4	–	–	88.7	–	–	0.784
Smoker (%)	65.4	–	–	76.2	–	–	62.1	–	–	46.6	–	–	<0.001
AFC	14.7±4.7	14.0	18	14.1±3.8	14.0	17	14.5±4.7	12.0	18	16.5±5.0	17.5	15	0.0001

ANOVA performed for statistical analysis for donor age.
Linear regression performed for statistical analysis for AFC with the confounding factors being age and smoking.
The χ^2-test performed for statistical analysis for proven fertility and smoking status.
AFC, antral follicle count; ANOVA, analysis of variance.

$P < 0.001$). The number of days of stimulation was correlated with the N680S FSHR polymorphism. The days of stimulation for women from the NS (11.4±1.8) and NN (11.4±1.6) groups were lower compared with the SS group (11.8±1.3) ($P < 0.001$). Fig. 1 shows the box plots for the amount of gonadotropin used, stimulation length, and retrieved oocytes among the women with the *FSHR* genotype.

Cycle outcome

The egg donation treatment outcomes are given in Table 3. We have compared the results between the genotypes (SS, NS, and NN). Overall, 355 COH cycles were considered for this study and no significant differences in the cycle outcome were observed between the genotypes (Table 3). No differences were observed in the recipient patient's age (40.7± 4.2 for SS, 41.1±4.4 for NS, and 39.9±4.8 for NN; $P = 0.074$), endometrial thickness (8.8±1.7 for SS, 8.4±1.6 for NS, and 9.2±1.5 for NN; $P = 0.310$), days of hormone replacement therapy (19.2±4.2 for SS, 18.5±3.8 for NS, and 18.8±4.1 for NN; $P = 0.420$), number of oocytes received (12.8± 3.0 for SS, 12.9±4.0 for NS, and 13.4±3.6 for NN; $P = 0.467$), fertilization rate ($P = 0.501$ for conventional IVF and $P = 0.706$ for intracytoplasmic sperm injection), fertilization technique, or the day of embryo transfer (data not shown). There were no significant differences with respect to biochemical pregnancy (70.0% for SS, 70.2% for NS, and 65.2% for NN; $P = 0.731$), the ongoing pregnancy rate (56.2% for SS, 55.6% for NS, and 47.0% for NN; $P = 0.410$), miscarriage rate (13.3% for SS, 8.3% for NS, and 16.1% for NN; $P = 0.419$), and implantation rate (41.6% for SS, 41.6% for NS, and 34.1% for NN; $P = 0.161$).

Discussion

To our knowledge, these data show for the first time the relation between the FSHR N680S polymorphism and ovarian stimulation and clinical outcome using a non-confounding model of egg donation. Our data suggest that the AFC and ovarian stimulation are affected by polymorphisms of the *FSHR* gene. The number of oocytes yielded, the days of stimulation, and the gonadotropin dosage are associated with the genotype in the N680S polymorphisms of the *FHSR* gene. In contrast, in previous studies, the clinical outcome was not reported to be associated with the genotype of the S680 polymorphisms.

The genotypic variance of *FSHR* was reported for the first time by Aitomäki *et al.* [22] in 1995. Thereafter, the possibility of whether polymorphisms of the *FSHR* gene affect the ovarian response to exogenous gonadotropins has been considered. Perez Mayorga *et al.* [17] studied 161 infertile women undergoing IVF and observed that the SS genotypes require higher gonadotropin doses and have higher basal FSH levels compared with other genotypes. Jun *et al.* [23] reported a higher dose of gonadotropin for the SS group compared with other groups and higher oocyte retrieval and pregnancy rates for the NN group compared with the other groups. Similarly, Sudo *et al.* [24], De Castro [25], and a recent study published by Sheikhha *et al.* [26] reported the same results. Interestingly, corroborating with these studies, our study shows that in the SS group, the gonadotropin dose is higher and the oocytes retrieved are lesser compared with the other genotype groups. The higher gonadotropin consumption in the SS group could be explained by the fact that patients with the SS genotype have increased basal FSH levels and tend to require large FSH doses, as reported in the meta-analysis by Yao and colleagues. These findings imply that women with the SS variant of the receptor are more resistant to FSH action compared with women carrying the others variants [24,26,27]. However, Yao and colleagues did not find an association between the number of oocytes and genotype. One explanation for this might be that there is a reflection of the IVF procedure: the FSH dose of poor responders is raised to achieve an adequate number of eggs and the dose of good responders is lowered to avoid hyperstimulation. The only clinical trial on the gene variants and COH outcome carried out so far has confirmed the previous finding of the effect of the N680S polymorphism, indicating that the lower FSH sensitivity of the SS carriers may be overcome by administering higher FSH doses during the COH protocols [18].

COH is a crucial step in ART. Successful outcomes after ART are largely dependent on the patient's response to controlled COH. Moreover, the risk of an inadequate

Table 2 Donor ovarian stimulation data in relation to the *FSHR* S680 genotype

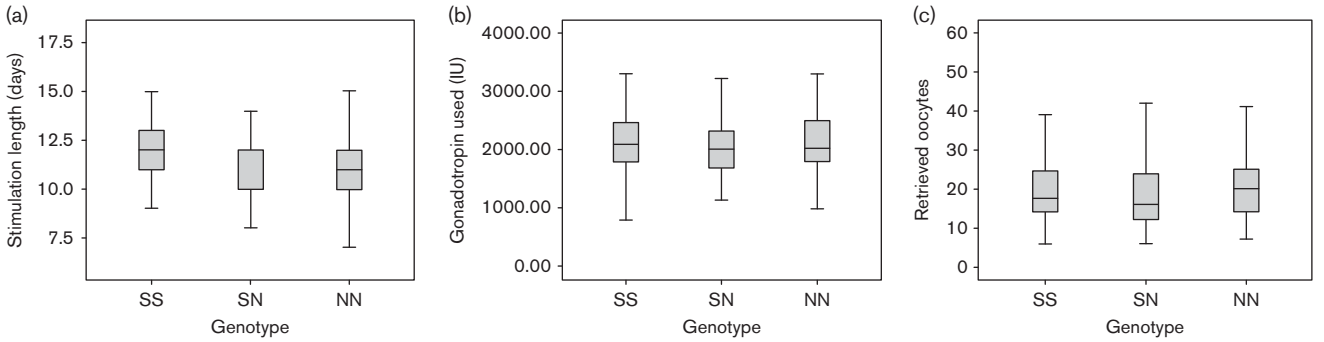
FSHR N680S genotype	Total (355)			SS (151)			NS (142)			NN (62)			*P* (unadjusted)	*P* (adjusted)	*P* (age-adjusted)	*P* (fertility-adjusted)	*P* (smoker-adjusted)	*P* (AFC-adjusted)
	Average±SD	Median	Range	Average±SD	Median	Range	Average±SD	Median	Range	Average±SD	Median	Range						
Stimulation length (days)	11.6±1.6	12.0	11	11.8±1.3	12.0	6	11.4±1.8	11.0	10	11.4±1.6	25.0	12	0.026	<0.001	0.007	0.048	0.008	0.035
Gonadotropin used (IU)	2090.2±546.5	2025.0	3300	2149.5±552.3	2100	2725	2023.5±490.1	2025.0	3300	2098.5±639.4	17.5	15	0.142	<0.001	<0.001	0.268	0.021	0.005
Number of retrieved oocytes	19.6±8.7	18.0	53	19.8±8.9	18.0	53	18.5±8.2	17.0	41	21.5±9.2	11.0	9	0.062	<0.001	0.098	0.001	0.322	0.008

Linear regression performed for statistical analysis using the SS genotype as a reference.
AFC, antral follicle count.

response to stimulation requiring cycle cancellation is probable. To improve the chances of a successful outcome, the doses should be tailored according to the patient's characteristics. There are several factors that can predict the ovarian response, such as age [8], ovarian reserve [9], hormonal status [10], and cigarette smoking [11]. The ovarian reserve is probably the most important factor in determining the success rates after IVF. The gonadotropin dose for ovarian stimulation usually increases with decreasing ovarian reserve, though it is unknown whether such increases in stimulation improve the oocyte yield. However, a recent meta-analysis has reported that markers of the ovarian reserve have only a modest role in predicting the response to gonadotropins [28]. From this assumption, recent research has attempted to show an association between the *FSHR* genotype and ovarian reserve markers such as antimüllerian hormone (AMH) and AFC [19,20] but could not prove it. This is not surprising, given that the ovarian reserve consists of primordial follicles that are not activated by FSH, and the expression of FSHR is not relevant to these follicles [29]. As regards the serum levels of AMH and the *FSHR* genotype, a recent study reported that AMH decreases the expression of gonadotropin-stimulated aromatase and surprisingly also reduces the expression of FSHR mRNA [30]. Therefore, AMH inhibits factors affecting FSH sensitivity [30]. Moreover Greb *et al.* [31] reported that women with the SS genotype had an earlier drop during the luteal secretion for products such as estradiol, progesterones, and inhibin A, a fact that was associated with the earlier regression of the corpus luteum. As a consequence of this decreased negative feedback of luteal secretion to the pituitary, FSH secretion rose earlier, and this rise appeared to remain constant throughout the follicular phase. Surpassing the FSH threshold level stimulates and prolongs the FSH-dependent phase of follicular maturation early on; this may explain the increased number of visible antral follicles in women with the SS genotype according to the basal FSH levels. Oocyte donation is the best model to evaluate the determinants of stimulation and embryo implantation potential. Donors are young women of similar age with a normal ovarian function and, in our egg donation program, with previously proven fertility. Our data suggest that, in our study population, different AFCs are observed between the different genotype groups. NN patients have higher AFCs compared with other genotypes. Our results disagree with those of the previous studies. One explanation is the heterogeneity between the infertile patients in the previous studies and the homogeneity of the characteristics of the patients in the present study, mainly with respect to age.

The question of whether genetic variation in *FSHR* is associated with pregnancy rates remains controversial [2,18,23,32] and requires further studies on large populations. Our data suggest that there is no difference

Fig. 1



Boxplots for the ovarian stimulation data among the FSHR genotypes showing medians, quartiles, and ranges of (a) stimulation lengths (b) gonadotropin used, and (c) number of retrieved oocytes.

Table 3 Recipient characteristics and cycle outcomes according to the egg donor's genotype

	Total (355)			SS (151)			NS (142)			NN (62)			
FSHR N680S genotype	Average±SD	Median	Range	Average±SD	Median	Range	Average±SD	Median	Range	Average±SD	Median	Range	*P*
Recipient age (years)	40.8±4.4	42.0	27	40.7±4.2	42.0	25	41.4±4.4	42.0	21	39.9±4.8	40.0	25	0.074
Follicular phase length (days)	18.8±4.1	18.0	23	19.1±4.2	19.0	22	18.5±3.9	18.0	21	18.8±4.2	19.0	25	0.420
Recipient endometrial thickness (mm)	8.7±1.6	8.3	7	8.8±1.7	8.8	6	8.4±1.6	8.0	7	9.2±1.5	9.0	5	0.310
Number of oocytes received	12.9±3.5	12.0	25	12.8±3.0	12.0	21	12.9±4.0	12.0	25	13.4±3.6	12.0	17	0.467
2PN conventional IVF	7.4±4.8	8.0	17	7.0±4.1	7.0	14	7.8±3.6	8.0	17	7.3±3.9	7.50	15	0.501
2 PN ICSI	8.3±3.1	8	16	8.3±2.8	8.0	16	8.4±3.8	12.0	25	8.0±3.4	8.0	14	0.706
Transferred embryos	1.8±0.5	2.0	3	1.8±0.4	2.0	3	1.9±0.4	8.0	17	1.9±0.5	2.0	2	0.217
Positive β-HCG (%)	69.0	–	–	70.0	–	–	70.2	–	–	65.2	–	–	0.731
Clinical pregnancy rate (%)	54.0	–	–	56.2	–	–	55.6	–	–	47.0	–	–	0.410
Implantation rate (%)	39.4±41.8	–	–	41.6	–	–	41.6	–	–	34.1	–	–	0.161
Miscarriage rate (%)	12.0	–	–	13.3	–	–	8.3	–	–	16.1	–	–	0.419

Test performed for statistical analysis ANOVA.
ANOVA, analysis of variance; HCG, human chorionic gonadotropin; ICSI, intracytoplasmic sperm injection.

between the genotypes, but our results come from an egg donation program and the effect of the genotype is not related to embryo implantation.

The assumption that the application of pharmacogenetics to the problem of searching markers to measure the ovarian reserve and predicting the ovarian response may predict treatment response is true [12]. However, a clinical disorder in an individual is not the product of a single gene disruption; it is embedded in the context of that individual's entire genome and environment [33]. In fact, some other genes related to follicular growth could also play an important role in determining the response to COH. Other factors such as polymorphisms of the α and β estrogen receptors and CYP19 aromatase [25] and the bone morphogenetic protein 15 (BMP15) [34] could be related to the response to exogenous FSH. The search for optimal biomarkers is ongoing for an accurate prognosis of the ovarian response to exogenous gonadotropins [35].

Conclusion

This investigation reveals that in a population of fertile egg donors, the FSHR gene polymorphism at position 680 is associated with different ovarian responses to COH. The genotype of the *FSHR* gene is an important factor in determining the prognosis of the COH cycles on fertile women with normal ovulation. Genotyping the FSHR N680S together with some additional markers may therefore provide a means of identifying a group of poor responders before infertility treatment is initiated.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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