The role of gonadotropin polymorphisms and their receptors in assisted reproductive technologies and controlled ovarian stimulation: a prospective observational study

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ABSTRACT

Introduction: individualized controlled ovarian stimulation (iCOS) is attracting great interest in the field of reproductive endocrinology. Although functional and hormonal markers (i.e., antral follicle count and antimullerian hormone) are now considered for iCOS, the validity of using specific genotype profiles to further refine this approach remains unknown. Specifically, some polymorphisms seem to significantly influence the ovarian response to gonadotropin; however, the broad clinical significance of these findings is unclear.

The aim of the present study is to establish whether specific polymorphisms of gonadotropin and their receptors could influence COS in women undergoing IVF/ICSI cycles.

Methods: a prospective observational study in normogonadotropic IVF/ICSI patients admitted to Federico II IVF Unit was carried out. Only normogonadotropic caucasian women fulfilling the following inclusion criteria were enrolled: age 20–34 years; BMI 20–27 kg/m2; basal FSH ≤ 10 IU/l; functional ovaries. Exclusion criteria were: uterine anomalies; endocrine, genetic or immunological disorders; PCOS; history of impaired ovarian response (≤ 4 oocytes retrieved) in at least one IVF/ICSI cycle. Patients underwent a GnRH long down-regulation protocol with fixed starting dose of 150 IU of recombinant FSH daily. Four single nucleotide polymorphisms (SNPs) were genotyped: FSH-Receptor variant (rs6166), FSH β subunit variant (rs6169). FSH-Receptor variant (rs6165); LH β subunit variant (rs1800447).

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SOMMARIO

Introduzione: la stimolazione ovarica controllata individualmente (iCOS) sta attirando un grande interesse nel campo dell'endocrinologia riproduttiva. Anche se i marcatori funzionali e ormonali (es. numero di follicoli antrali e l'ormone antimulleriano) sono ora considerati per la iCOS, la validità dell'utilizzare profili specifici di genotipo per perfezionare ulteriormente questo approccio rimane sconosciuta. In particolare, alcuni polimorfismi sembrano influenzare in modo significativo la risposta ovarica alla gonadotropina. Tuttavia, l'ampio significato clinico di questi risultati non è ancora chiaro.

Lo scopo di questo studio è quello di stabilire se i polimorfismi specifici della gonadotropina e dei loro recettori possano influenzare la stimolazione ovarica controllata nelle donne sottoposte a cicli IVF/ICSI.

Metodi: è stato condotto uno studio di osservazione prospettico nei pazienti normogonadotropici IVF/ICSI ammessi all'Unità IVF dell'Università di Napoli Federico II. Sono state iscritte solo donne normogonadotropiche caucasiche che soddisfassero i seguenti criteri: età 20-34 anni; BMI 20-27 kg/m2; FSH basale ≤ 10 IU/l; ovarie funzionali. I criteri di esclusione erano: anomalie uterine, disturbi endocrini, genetici o immunologicid, PCOS, storia di alterazione della risposta ovarica (≤ 4 oociti recuperati) in almeno un ciclo IVF/ICSI. I pazienti sono stati sottoposti a un lungo protocollo di abbassamento GnRH con dose fissa iniziale di 150 UI di FSH ricombinante giornaliera. Sono stati genotipati quattro polimorfismi nucleotidi singoli (SNP): variante FSH-Receptor (rs6166), variante subunità di FSH β (rs6169), variante FSH-Receptor (rs6165) e variante subunità LH β (rs1800447).

Risultati: sono stati selezionate complessivamente 30 donne. Tutti i genotipi rientravano nell'equilibrio di Hardy Weinberg. I polimorfismi FSH-Receptor rs6165 e rs6165 erano in forte disequilibrio di collegamento (p <0,05).

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Results: a total of 30 women were selected. All genotypes were in Hardy Weinberg equilibrium. FSH-Receptor polymorphisms rs6165 and rs6165 were in strong linkage disequilibrium (p < 0.05). LH β subunit variant (rs1800447) heterozygotes A/G showed lower number of fertilized oocytes compared with homozygotes A/A and this difference almost reach statistical significance (1.8 ± 0.4 vs 2.2 ± 0.8; p = 0.08). Regarding FSH-Receptor genotype (rs6166), a post hoc analysis revealed lower number of oocytes retrieved in allele T homozygotes carriers comparing with C/T heterozygotes (5.4 ± 2.4 vs 9.5 ± 3.0; p < 0.05) and allele C homozygotes carriers (5.4 ± 2.4 vs 8.8 ± 3.4; p = 0.15). Differences in terms of number of follicles ≥ 16mm were also observed in T allele homozygotes carriers comparing to C/T (5.6 ± 2.1 vs 9.6 ± 2.2; p < 0.05) and C/C (5.6 ± 2.1 vs 9.2 ± 2.9; p < 0.05) carriers.

With respect of FSH-β subunit polymorphism (rs 6169), no differences in terms of ovarian response and IVF outcome was observed.

Co-expression of FSH-Receptor allele T, LH β subunit allele G and FSH β subunit allele T variants lead to a significant reduction of the number of oocytes retrieved (p = 0.038).

Discussion: although limited by the small size of population recruited, these findings confirm that specific polymorphisms of gonadotropin and their receptors could affect ovarian response to COS in IVF cycles. These data support the concept that the ovarian response to exogenous FSH seems to be determined by the interaction of specific genetic traits. If our data will be confirmed by further investigation a pharmacogenomic approach to COS could be hypothesized.

La variante della subunità LH β (rs1800447) ha mostrato un minor numero di oociti fecondati rispetto agli omozigoti A / A e questa differenza raggiunge quasi il livello di rilevanza statistica (1,8 ± 0,4 vs 2,2 ± 0,8, p = 0,08). Per quanto riguarda il genotipo FSH-Receptor (rs6166), un'analisi a posteriori ha rivelato un minor numero di oociti recuperati nei vettori omozigoti di allele T confrontati con eterozigoti C / T (5,4 ± 2,4 vs 9,5 ± 3,0, p <0,05) e vettori omozigoti di allele C ± 2,4 vs 8,8 ± 3,4, p = 0,15). Le differenze in termini di numero di follicoli ≥ 16 mm sono state osservate anche nei vettori omozigoti T allele rispetto a C / T (5,6 ± 2,1 vs 9,6 ± 2,2, p <0,05) e C / C (5,6 ± 2,1 vs 9,2 ± 2,9, p < 0,05).

Con riferimento al polimorfismo della subunità FSH-β (rs 6169), non sono state osservate differenze in termini di risposta ovarica e risultato dell'IVF.

La coespressione dell'allele FSH-Receptor allele T, dell'allele subunità G allele LH β e delle varianti T allele subunità di FSH β portano ad una significativa riduzione del numero di oociti recuperati (p = 0,038).

Discussione: sebbene limitati dalla piccola dimensione di popolazione reclutata, questi risultati confermano che specifici polimorfismi di gonadotropina e dei loro recettori potrebbero influenzare la risposta ovarica alla COS nei cicli IVF. Questi dati supportano il concetto che la risposta ovarica a FSH esogeno sembra essere determinata dall'interazione di specifici tratti genetici. Se i nostri dati saranno confermati con ulteriori indagini, potrebbe essere ipotizzato un approccio farmacogenoico al COS.

INTRODUCTION

Individual response to control ovarian stimulation (COS) represents a topic a great interest in reproductive field. In the past, ovarian stimulation approach was based only on demographic and anthropometric characteristics of women. Now, the introduction in clinical practice of ovarian reserve markers such as antral follicles count and anti-mullerian hormone has considerably improved our approach to infertile women. Some author have also developed a specific a model to establish the right IVF protocol on the basis of ovarian reserve test[1]. Such tailored approach to COS is crucial to maximize results, manage the risk and optimize the cost/effectiveness profile.

Apart from ovarian reserve, there is evidence that individual genotype profile could also influence ovarian response to COS[2-5]. Several polymorphisms of gonadotropins and their receptors have been identified. Most of variants consist in single-base changes, known as single nucleotide polymorphisms (SNPs). Genetic variation is considered an SNP when it occurs in a frequency higher than 1% mutation is higher than 1%[5]. More than 3 million of polymorphisms in human genome have been identified and the number will probably increase in near the future[6].

On the basis of the current literature, it is possible to argue that inappropriate response to ovarian stimulation could be linked to specific gonadotropin and their receptor polymorphisms[4, 7]. The most interesting polymorphisms involved common variants of LH β subunit and FSH receptors (FSH-R).

In detail, a common LH β variant (rs1800447), was associated with impaired ovarian response to in several studies[4, 8]. This genotype seems to be significantly widespread in different ethnical groups. In Italy, it was estimated that the carrier frequency of this polymorphic variant

is approximately 14%[4]. This polymorphism is characterized by an extra glycosylation signal into the β subunit, which apparently adds a second oligosaccharide side-chain to Asn13 of the β protein. This molecular variation influences the pharmacokinetic properties of v-βLH which shows an elevated bioactivity in vitro, but a significantly shorter half-life (26 min) when compared with the wild type LH (48 min)[9].

The most investigated polymorphism of the FSH-R consists in the replacement at position 680 of the amino acid asparagine by serine (rs6166)[10]. This polymorphism is also worldwide distributed with predominance of derived allele C (Ser) among Kalash, Melanesian and Surui people and allele T (Asn) in Southeastern Asia[11]. This polymorphism has also been associated with higher basal FSH levels anomalous response to exogenous gonadotropin[3, 12, 13].

With the aim to evaluate the impact and the interaction between polymorphisms of gonadotropins and their receptors on COS and IVF/ICSI success, we developed an observational prospective trial.

METHODS

Candidates for IVF/ICSI cycles at Federico II IVF Unit were assessed for eligibility. The following inclusion criteria was adopted: age between 20 and 40 years; body mass index (BMI) $\geq$ 20 and $\leq$ 35 kg/m2; basal FSH $\leq$ 12 IU/l; presence of both functional ovaries. Women with the following characteristics were excluded: anomalies of the uterine cavity; genetic or systemic inflammatory-immunological disorder; diabetes type I and II; ovarian cysts. Furthermore, women with polycystic ovarian syndrome (Rotterdam criteria, 2004)[14], endometriosis and history of more than two previous IVF/ICSI cycles with normal ovarian response or previous stimulation cycle which had been cancelled for insufficient ovarian response (<4 oocytes retrieved) were not enrolled.

All patients provided written informed consult, which allows for the scientific purpose of medical record if they remains confidential and identity protected. Local institutional board and Ethic committee supervised the project.

All women enrolled underwent a gonadotropin releasing hormone agonist (GnRH-a) long down-regulation protocol with buserelin acetate as follows: 0.5 mg s.c. daily from the mid-luteal

phase for 12-14 days, after which the dose was reduced to 0.2 mg. After 14 days, transvaginal-ultrasonographic and biochemical evaluations were carried out only women with serum E2 level < 40 pg/ml, endometrial thickness <5 mm, and arrested follicular development were admitted for controlled ovarian stimulation. Women with delayed suppression (including subjects who develop ovarian cysts after the GnRH-a administration) were excluded. A fixed starting-daily dose of 150 of recombinant FSH (rFSH) was established for all participant. The starting gonadotropin dose was maintained for four days. E2 serum levels was measured on day five of stimulation. On that day, the daily dose of gonadotropin was modified only in women having E2 concentration >180 pg/ml. Only in these cases, according standard clinical practice, a daily dose of rFSH of 112.5 IU was adopted. Follicular growth was evaluated by on day 8 of stimulation by transvaginal ultrasound. Only patients who displayed at least 6 follicles ranging between 6 and 10 mm, but no follicle with a mean diameter >10 mm received an increase in the daily gonadotropin dose. Specifically, the dose of rFSH was increased by 150 IU per day, giving a cumulative daily dose of 300 IU. Women who had their daily dose of gonadotropin reduced on the fifth day of stimulation and who required a new increase on day 8 was excluded from the observation. Analogously, women who required "coasting" for reducing the risk for ovarian hyperstimulation syndrome (OHSS) was not included in this study. E2 serum levels were measured on days 1, 5, 8 of stimulation and on the day of human chorionic gonadotropin (hCG) administration. The ovulatory dose 10,000 IU of human choronic gonadotropin (hCG) or 250 mcg of recombinant human gonadotropin (r-hCG) was administered in the presence of three follicles with a mean diameter of at least 17 mm according to clinical practice. Oocytes was retrieved by transvaginal ultrasound-guided aspiration 34-36 hours after the hCG injection. Luteal phase support was given vaginally in the form of 400 mg micronized progesterone twice daily, until the day of the pregnancy test (i.e. day 12 after embryo transfer). The viability of pregnancy was confirmed by ultrasound scan at 10 weeks.

Primary endpoint was the number of oocyte retrieved. Secondary endpoints were: total dosage of rFSH administrated, duration of stimulation, number of follicles $\geq$ 16mm on day of triggering, number of oocytes retrieved, number of mature

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oocytes, number of fertilized oocytes, duration of stimulation, number of embryo transferred, pregnancy rate and ongoing pregnancy rate.

Sampling and polymorphisms analyses

Blood samples was collected for evaluating the presence of polymorphisms. The venous blood (10 ml) was allowed to clot and was centrifuged at 400 g for 10 min. Serum was separated, divided into a maximum of four aliquots and frozen. Pellets was divided in four aliquots and stocked at -80°C to be successively evaluated.

The PCR-based Custom TacMan® DNP Genotyping Assay (Applied Biosystems) was used to assess the following polymorphisms: FSH-R variant rs6165; FSH-R variant rs6166, FSH β subunit variant rs6169; LH β subunit variant rs1800447.

STATISTICAL ANALYSIS

Genotype frequencies of SNPs evaluated was obtained by direct computing. Hardy-Weinberg equilibrium and frequencies of enrolled patients were evaluated using Chi-square test. Differences of continuous variables among groups were evaluated performing ANOVA (more than two groups) or t student test (maximum two groups). Differences of categorical variables were tested using Chi square test. Statistical analysis was performed using the SPSS software (Statistical Package for the Social Sciences version 22, IBM, USA). Bonferroni test was adoped for post hoc evaluation of continuous variables. We assumed significance at the 5% level ($p < 0.05$).

RESULTS

A total of 30 women were enrolled according inclusion and exclusion criteria. All women were monitored during COS in which the following parameters were evaluated: total dosage of rFSH administrated, duration of stimulation, number of follicles ≥ 16mm on day of hCG triggering, number of oocytes retrieved, number of mature oocytes, number of fertilized oocytes, duration of stimulation, number of embryo transferred, pregnancy rate and ongoing pregnancy rate. Differences in terms of basal characteristics, such as age, BMI, basal FSH and basal estradiol were also measured.

In Table 1 are depicted genotype distribution of population study. No Allele G homozygotes of LH

β variants were detected in our population study. All genotypes analysed were in Hardy Weinberg equilibrium. It was assessed using a Chi Square test that did not reach statistical significance ($p > 0.05$). (**Table 1**).

Table 1.
Genotypes distribution and Hardy Weinberg equilibrium evaluation

SNP	Allele	Patients (%) N=30	Hardy-Weinberg equilibrium	p value
FSH-R rs6165	C/C	9 (30%)	YES	0.81
	C/T	16 (53.3%)		
	T/T	6 (20%)		
FSH-R rs6166	C/C	9 (30%)	YES	0.81
	C/T	16 (53.3%)		
	T/T	5 (16.7%)		
FSH β subunit rs6169	C/C	6 (20%)	YES	0.46
	C/T	17 (56.7%)		
	T/T	7 (23.3%)		
LH β subunit rs1800447	A/A	23 (76.7%)	YES	0.47
	A/G	7 (23.3%)		
	G/G	0		

Both polymorphisms rs6165 and rs6165 genotypes were in strong linkage disequilibrium ($p < 0.05$).

Population study, was stratified according genotype distribution for each polymorphism.

Comparable age, BMI, basal FSH and basal estradiol were observed in both heterozygote A/G and homozygote of A/A of LH β subunit variants rs1800447 (**Table 2**).

Table 2.
General characteristics and IVF outcome according rs1800447 genotype profile

	A/A	A/G	p value
Age (years)	30.9 ± 3.9	31 ± 2.6	NS
BMI (Kg/m^2)	23.1 ± 2.2	22.7 ± 2.5	NS
Basal FSH (IU/L)	6.64 ± 2.2	7.5 ± 1.9	NS
Basal estradiol (pg/ml)	66.8 ± 45.2	40.2 ± 22.0	NS
Total rFSH administrated (IU)	1644.9 ± 473.3	1650 ± 273.9	NS
Duration of stimulation (day)	11 ± 1.4	11.1 ± 1.5	NS
Follicles ≥ 16mm	8.4 ± 2.6	9.8 ± 3.1	NS
Oocytes retrieved	8.8 ± 3.3	8 ± 3.6	NS
Mature oocytes	7.5 ± 3.1	6.3 ± 3.5	NS
Oocytes fertilized	2.2 ± 0.8	1.8 ± 0.4	0.08
Embryo transferred	2.1 ± 0.8	1.9 ± 0.4	NS
Pregnancy rate (%)	34,7%	57.1%	NS
Ongoing pregnancy rate (%)	26.1%	28,6%	NS

continuous data are presented as mean ± standard deviation
categorical data are presented as percentage
NS: no statistical significance

No differences were also observed with respect of total rFSH administrated, duration of stimulation, number of follicles ≥ 16mm at day of

triggering, number of oocytes retrieved, mature oocytes and embryo transferred (Table 2). On the other hand, heterozygotes A/G showed lower number of fertilized oocytes compared with homozygotes AA and this difference almost reach statistical significance (1.8 ± 0.4 vs 2.2 ± 0.8; p =0.08) (Table 2). No differences were observed in terms of pregnancy and ongoing pregnancy rate among groups (Table 2).

With respect of FSH β subunit polymorphism (rs6169), no differences were detected regarding basal characteristics (Table 3). In the same line are results obtained during COS where no significant differences were observed in terms of total rFSH administrated, duration of stimulation, number of follicles ≥ 16mm at day of triggering, number of oocytes retrieved, mature oocytes, fertilized oocytes and embryo transferred. Comparable ongoing pregnancy rate and live birth rate were observed regardless genotype distribution (**Table 3**).

Table 3.
General characteristics and IVF outcome according rs6169 genotype profile

	C/C	C/T	T/T	p value
Age (years)	31.2 ± 3.4	31.7 ± 4.1	29 ± 1.9	NS
BMI (Kg/m^2)	22.1 ± 0.8	23.1 ± 2.5	23.6 ± 2.2	NS
Basal FSH (IU/L)	7.8 ± 1.9	7.01 ± 1.8	5.6 ± 2.7	NS
Basal estradiol (pg/ml)	50.6 ± 37.7	73.8 ± 50.5	44.5 ± 13.7	NS
Total rFSH administrated (IU)	1775 ± 718.8	1605 ± 387.2	1628 ± 179.9	NS
Duration of stimulation (day)	11.3 ± 2.1	11 ± 1.3	10 ± 0.9	NS
Follicles ≥ 16mm	9.6 ± 2.7	8.1 ± 2.7	9.4 ± 2.7	NS
Oocytes retrieved	9.5 ± 2.8	8.0 ± 3.4	9.5 ± 8.0	NS
Mature oocytes	7 ± 3.4	6.8 ± 3.2	8.3 ± 3.3	NS
Oocytes fertilized	2.2 ± 0.4	2.1 ± 0.8	2.2 ± 0.7	NS
Embryo transferred	2.2 ± 0.4	1.9 ± 0.8	2.3 ± 0.7	NS
Pregnancy rate (%)	66%	23.5%	57%	NS
Ongoing pregnancy rate (%)	50%	17.6%	28.5%	NS

continuous data are presented as means ± standard deviations
categorical data are presented as percentages
NS: no statistical significance

Both FSH-R polymorphisms (rs6165, rs6166) showed the same distribution in our population study considering that are in significantly strong linkage disequilibrium according our findings. Basal characteristics and COS outcomes of both polymorphisms stratified according genotype characteristics (C/C, C/T and T/T) are reported in **Table 4**. No differences was detected with respect of age basal FSH and basal estradiol comparing all genotype profiles (C/C vs C/T vs T/T). Only BMI was statistically differences among groups (p < 0.05). Differences in terms of number of follicles ≥ 16mm were observed in

Table 4.
General characteristics and IVF outcome according rs6165/rs6166 genotype profile

	C/C	C/T	T/T	p value
Age (years)	29.8 ± 2.6	31.5 ± 4.5	31.8 ± 1.6	NS
BMI (Kg/m^2)	21.7 ± 1.5	22.9 ± 1.7	26.02 ± 2.4	0.01
Basal FSH (IU/L)	7.3 ± 1.9	6.9 ± 2.2	5.7 ± 1.9	NS
Basal estradiol (pg/ml)	76.7 ± 1.9	6.9 ± 2.3	5.7 ± 1.9	NS
Total rFSH administrated (IU)	1568 ± 332.9	1618 ± 511.2	1870 ± 270.6	NS
Duration of stimulation (day)	10.5 ± 1.3	11.1 ± 1.5	11.6 ± 1.1	NS
Follicles ≥ 16mm	9.2 ± 2.9	9.6 ± 2.2	5.6 ± 2.1*	0.01
Oocytes retrieved	8.8 ± 3.4	9.5 ± 3.0	5.4 ± 2.4§	0.045
Mature oocytes	7.6 ± 3.6	7.5 ± 3.08	4 ± 0.0	NS
Oocytes fertilized	2.3 ± 0.9	2.1 ± 0.4	1.8 ± 1.3	NS
Embryo transferred	2.11 ± 0.6	2.06 ± 1.80	1.8 ± 1.3	NS
Pregnancy rate (%)	33.3%	50%	20%	NS
Ongoing pregnancy rate (%)	11.1%	37.5%	20%	NS

continuous data are presented as mean ± standard deviation
categorical data are presented as percentage
NS: no statistical significance
* T/T vs C/T - C/C: *p* < 0.05 Bonferroni *post hoc* test
§ T/T vs C/T - *p* < 0.05 Bonferroni *post hoc* test

T allele homozygotes carriers comparing to the other groups. A Bonferroni post hoc test showed a significantly lower values among allele T homozygotes groups comparing with both allele C heterozygotes (5.6 ± 2.1 vs 9.6 ± 2.2; p < 0.05) and homozygotes groups (5.6 ± 2.1 vs 9.2 ± 2.9; p < 0.05). Similarly, the number of oocytes retrieved was lower in allele T homozygotes comparing with both heterozygotes C/T (5.4 ± 2.4 vs 9.5 ± 3.0; p < 0.05) and allele C homozygotes (5.4 ± 2.4 vs 8.8 ± 3.4; p = 0.15). No differences among groups was observed with respect of total dosage of rFSH administrated, duration of stimulation, number of mature oocytes, number of fertilized oocytes and number of embryo transferred. Comparable pregnancy rate and ongoing pregnancy rate were observed regardless genotype profile.

A combined analysis of FSH-R (rs6166), FSH β subunit (rs6169) and LH β subunit (rs1800447) variant was carried out. Co-expression of FSH-R allele T, LH β subunit allele G and FSH β subunit allele T variants lead to a significant reduction of the number of oocytes retrieved (p = 0.038).

DISCUSSION

The understanding of the role of specific genetic polymorphism could open a new scenario in ART, with the opportunity to offer a tailored approach to single patients based on personal genotype profile.

Although limited by small sample size, our

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results demonstrate that FSH-R polymorphisms (rs 6165 - rs6166) and LH β variant (rs1800447) could influence ovarian response to exogenous gonadotropin. Specifically, relevant differences were observed regarding primary outcome (number of oocytes retrieved), number of follicles recruited during COS and number of fertilized oocytes. On the other hand, no effect of FSH β subunit variant (rs6169) was observed on COS or IVF outcome.

Moreover, we also investigated how the interaction of the investigated polymorphisms could influence ovarian response. Specifically, the combined analysis of FSH-R, LH β variant and FSH β variant, revealed that the co-expression of allele T, allele G and allele T respectively, significantly influences the number of oocytes retrieved (p = 0.038).

The strength of these observations is supported by the prospective design of our study and strictness of our enrollment criteria. In fact, we selected only normogonadotropic women expected to be normoresponder to COS with very strict inclusion and exclusion criteria, discharging any women at risk of hyper or poor response. In addition, women who showed a low-response or hyper-response profile during COS (i.e those who required "coasting" for OHSS risks, or those who demanded additional rFSH administration) were excluded from the study.

Both FSH and LH are required during folliculogenesis, and hence it is not surprising that variants of both gonadotropins could affect ovarian response to gonadotropin. The classical "two cells-two gonadotropins" model is based on the idea that FSH and LH exerts their roles on two different compartments, granulosa and theca, respectively. However, recently findings, have demonstrated that that LH receptors are also detected on the granulosa compartment at the intermediate follicular phase[15-17]. Therefore, it appears that LH could regulates both granulosa and theca cells. According this new model the proper function of both gonadotropins are mandatory for follicular growth and optimal reproductive outcome even in ART.

The effect of FSH-R polymorphism on COS (rs6169) was supported by several studies. In detail, this polymorphic variant of the FSH-R has been associated with higher FSH basal levels and increased number of antral follicles during the early follicular phase (Greb et al., 2005).

In a retrospective observational trial, Perez-Mayorga et al. (2000) evaluated the relationship between the presence. They demonstrated that FSH-R variant is able to influence the mean number of rFSH ampoules required for successful stimulation among different FSH-R genotype profiles. Recently, a study published by our groups demonstrated how this polymorphism is associated with hypo-response profile[3]. According our findings, FSH-R polymorphism influence ovarian response to exogenous gonadotropin in term of oocytes retrieved and number of follicles recruited during stimulation. Despite Perez Mayorga and Greb findings, we did not detect any differences regarding rFSH consumption for the inclusion criteria adopted which excluded any relevant modification in rFSH dosage during COS.

On the other hand, rLH β subunit polymorphism (rs1800447) seemed to influence the "quality" of oocytes with reduced number of fertilization oocytes in allele G carriers compared with wild type carriers.

In conclusion, if our findings will be confirmed by further investigations a pharmacogenomic tailored approach to COS could be hypothesized. For example, it was suggested that the assessment of genotype profile could lead clinician to an appropriate COS modifying starting rFSH dosage for those women who carried FSH-Rpolymorphic variant or adding recombinant LH for those patients who express common LH β polymorphism[18].

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CONFLICT OF INTEREST
None

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