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Short Communication

Polycystic ovary-like abnormalities and Single Nucleotide Polymorphisms as potential biomarkers for controlled ovarian stimulation outcome; A novel approach

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Abstract

Polycystic ovary – like (PCO-L) abnormalities is a condition characterized by normally menstruating cycles, sporadic anovulation and no known infertility. These women usually present with hyperandrogenism, without polycystic ovarian morphology. With the present study, we attempted to evaluate the role of single nucleotide polymorphisms of FSH and Estrogen Receptors to the outcome of assisted reproduction techniques, in patients with PCO-L. We demonstrated that certain genotypes lead to higher pregnancy rates. Further studies need to be made in order to clarify the ideal ovulation induction protocol in patients with PCO-L.

Key words: hyperandrogenism; polycystic ovary-like abnormalities; poor responders; single nucleotide polymorphisms; ovulation induction

Short communication

Polycystic Ovarian Syndrome (PCOS) is a common endocrinopathy, characterized by oligoovulation or anovulation, signs of androgen excess and multiple small ovarian cysts. Signs and symptoms present with high variability among each patient and also within individuals during different time periods. According to the Rotterdam ESHRE/ASRM Sponsored PCOS Consensus Workshop Group in 2004, affected individuals must have two of the following three criteria:

1. oligo- and/or anovulation,
2. hyperandrogenism (clinical and/or biochemical),
3. polycystic ovaries identified sonographically.

However, since there are other etiologies, such as congenital adrenal hyperplasia, androgen-secreting

Table 1: Demographic characteristics of PCO-L and Good Responders

Pregnanies - PCO - L (*n*= 4)			Pregnanies - Good Responders (*n*= 11)		
ESR1	CC= 0/4	0.00%	ESR1	CC= 2/11	18,20%
	CT= 3/4	75%		CT= 6/11	54,50%
	TT= 1/4	25%		TT= 3/11	27,30%
ESR2	GG= 4/4	100%	ESR2	GG= 11/11	100%
	GA= 0/4	0%		GA= 0/11	0%
	AA= 0/4	0%		AA= 0/11	0%
FSHR	SS= 1/4	25%	FSHR	SS= 3/11	27,30%
	SA= 3/4	75%		SA= 6/11	54,50%
	AA= 0/4	0.00%		AA= 2/11	18,20%

Table 2: Distribution of different genome variations between groups

	PCO -L (*n*= 20)	Good Responders (*n*= 28)
ESR1 - CC (%)	18.8	14.3
ESR1 - CT (%)	50	57.1
ESR1 - TT (%)	31.3	28.6
ESR2 - GG (%)	93.8	92.9
ESR2 - GA (%)	6.3	7.1
ESR2 - AA (%)	0	0
FSHR - Ser/Ser (%)	37.5	17.9
FSHR - Ser/Asn (%)	37.5	60.7
FSHR - Asn/Asn (%)	25	21.4

tumors, Cushing syndromeand hyperprolactinemia, that could lead to oligoovulation and/or androgen excess, PCOS is a diagnosis of exclusion.

Functional hypothalamic amenorrhea (FHA), a frequent cause of anovulation, is characterized by hypoestrogenism and negative energy balance due to excessive exercise and/or severe food restriction, leading to hypoinsulinism[1]. This leads to a hypogonadotropic state, affecting the secretion of LH, rather than FSH. Interestingly, polycystic ovarian morphology (PCOM) has been detected in 30-50% of patients with FHA[2]. It seems that asymptomatic women with PCOM have increased serum levels of Anti-Müllerian Hormone (AMH). AMH is a dimeric glycoprotein, produced exclusively in the ovary by the granulosa cells of preantral and small antral follicles[3].

The prevalence of polycystic ovary-like abnormalities (PCO-L) in the general population is around 30%. A mild PCO-like phenotype has also been described. These women have normally menstruating cycles with sporadic anovulation and no known infertility. It is associated with a greater LH to FSH ratio, greater follicular phase LH, lower SHBG and elevated fasting insulin[4].

The question that needs to be answered is what seems to be the optimal method for patients with hyperandrogenism and no PCOM, that present for infertility treatment.

In 2006, Loutradis et al., evaluated the frequency distribution of the Ser680Asn polymorphism of the follicle-stimulating hormone receptor (FSHR) gene in ovarian dysfunction (OD) infertile women, "poor

Table 3: Polygenic study of ESR1 FSHR in Good Responders group				
	Pregnancies (N=11)	**TOTAL (N= 28)**	**Pregnancies**	**No Pregnancies**
CC/SS	I	I	100%	
CC/SA	I	II	33.30%	66.60%
CC/AA	Not present in good responders			
CT/SS	I	I	100%	
CT/SA	**IIII**	**IIIIIIIII**	**30%**	**70%**
CT/AA	I	IIIII	20%	80%
TT/SS	I	III	33.30%	66,60%
TT/SA	I	IIII	25%	75%
TT/AA	I	I	100%	

The genetic profile of the women that had clinical pregnancy in each group,not considering each locus separately, but in combination to good responders

Table 3: Polygenic study of ESR1 and FSHR in PCO-L group					
	Pregnancies (N=4)	**No Pregnancies (N=16)**	**TOTAL (N= 20)**	**Pregnancies**	**No Pregnancies**
CC/SS		I	I	0%	100%
CC/SA		I	I	0%	100%
CC/AA		I	I	0%	100%
CT/SS	**III**	**III**	**IIIIII**	**50%**	**50%**
CT/SA		II	II	0.00%	100.00%
CT/AA		III	III	0%	100%
TT/SS		II	II	0%	100%
TT/SA	I	III	IIII	33.3%	95%
TT/AA	No expression				

The genetic profile of the women that had clinical pregnancy in each group, not considering each locus separately, but in combination to PCO-L

responders" (PR) and "good responders" (GR), aiming to assess whether FSHR gene polymorphisms have a role for different ovarian response in women entering controlled ovarian stimulation (COS) protocols. It was stated that GR patients carry more often the Asn/Ser genotype, which is correlated with a greater number of follicles and oocytes in both OD and GR women. Moreover, the Ser/Ser variant could be related to higher serum FSH levels, while the Asn/Ser with lower ones[5]. The findings of this study dictate that FSHR gene polymorphisms could serve as a biomarker to predict ovarian response in women entering IVF/ICSI-ET programs. Based on these results, and on the fact that individualization of treatment seems to be the key-factor to improve assisted reproduction techniques (ART), we conducted apreliminarystudy in order to analyze three different polymorphisms of ESR1, ESR2 and FSHR genes and to assess their involvement in ART outcome in Greek hyperandrogenic patients. We separated out patients into two groups: A) patients with hyperadrogenism, characterized as PCO-L (*n*=20) and B) GR who served as controls (*n*=28). The characteristics of each group are analyzed in Table 1. We re-

corded 4 pregnancies in the PCOS-Like group and 11 pregnancies in the control group. We analyzed the genetic profile of both groups (Table 2) and also that ofwomen that achieved clinical pregnancy in each group (Tables 3 & 4).

In a previous study by our group, we showed that-GRpatients with a genetic profile CT/SA had higher pregnancy rates. We also observed that CC/AA combination had poor prognosis and is not detected in the GR population, while hyperandrogenic patients with CT/SS genetic profile presented with high pregnancy rate (3/4). Based on our data, we came to the conclusion that a polygenic trait of ESR1, ESR2 and FSHR demonstrates convincingly that Single Nucleotide Polymorphisms (SNPs) genes can be used as biomarkers to predict ovarian response in hyperadrogenic PCO-Like patients[6].

The origin of PCO-L is not very clear. It seems that in cases where there is low serum LH and insulin levels, the androgenic dysfunction of PCO-L is driven by intraovarian factors. Moreover, there have been FHA cases reported, where an androgen excess inside the ovaries, independent from LH and insulin influence, could be the cause of PCO-L[7].

At this point, we need to clarify that in clinically normal adult women, the presence of PCO-L is not the cause of the development of PCOS. Diagnosing PCO-L in a woman with FHA does not necessarily qualify her for PCOS. However, there are patients that could develop PCOS, once serum LH and insulin levels return to normal[8].

Based on the findings of the present study, GRs have a higher expression of Ser/Asngenotype of theFSHR than patients with PCOS-L (60.7 and 37.5% respectively). On the other hand, PCOS-L group seems to have a higher expression of the Ser/Ser genotype of FSHR than GRs group (37.5 and 17.9 respectively). Regarding the ESR, we demonstrated that CT/SA genotype lead to more pregnancies in the GPs group and the CT/SS to an even number in both groups. Further studies need to be designed in order to explain the mechanisms that cause sporadic anovulation in PCO-L patients with hyperandrogenism, in an attempt to solve the mystery of ovulatory subfertility.

Conflict of interest

We declare that we have no conflict of interest.

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