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Article

# THE ROLE OF DETERMINANT GENES OF STEROID HORMONES DYSFUNCTION REGULATORS (CYP17A1-RS743572, CYP19A1-RS247015) IN THE DEVELOPMENT OF PCOS IN WOMEN WITH INFERTILITY

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**Summary. Purpose:** to develop prognostic criteria for the outcomes of ART programs in women with infertility in PCOS based on molecular genetic predictors of folliculogenesis disorders. **Material and research methods.** To solve the tasks set in the work, 125 women were examined: group first - 45 women with primary PCOS and infertility; group second - 46 women with infertility and PCOS in preparation for ART; group third 26 conditionally healthy women. Based on the foregoing, we presented the data of our own studies on the assessment of the state, the genes of steroid hormones (CYP17A1-rs743572, CYP19A1-rs247015) based on the analysis of laboratory data.

**Results and its discussion.** Regarding the influence of the polymorphism of the CY19A1 rs2470152 gene on the development of PCOS, mutant alleles were found to be significantly higher in patients than in the control group. When we divided the main group into MC(+) and MC(-) in terms of CYP19A1 and compared with the control group, we found that the homozygous mutant genotype was found to be greater in the MC(+) and MC(-) group compared to the control group. With this, we can conclude that the homozygous mutational form of the CYP19A1 gene plays a convincing inducible role in PCOS and our result was significant (chi2 - 5.74; $p<0.02$ in the main group; chi2=5.2; $p=0.02$ in patients with metabolic syndrome and chi2=3.9; $p<0.05$ in patients without metabolic syndrome). However, the study did not reveal an induced effect on the heterozygous genotype in the development of PCOS (chi2<3.85; $p>0.05$). At the same time, the wild-type homozygous variant played a protective role in terms of the appearance of PCOS in the main group, as well as in the MC (+) and MC (-) groups (OR≥0.5). When it comes to the Hardy Weinberg equation, we found no significant difference between the expected and observed results in the main group. Estimates of polymorphism prediction efficiency, as already mentioned, showed only 0.6, which means that the prediction efficiency was not reliable in terms of mutant allele and genotype.

**In conclusion**, from the study of CY17A1 polymorphism in patients with PCOS, it can be said that the GG mutant genotype was statistically significantly more common in patients compared to the control group. When dividing PCOS patients, they were divided into groups and compared with the control group, MS+ PCOS patients had a lower level of the mutant form (GG) genotype compared to the control group, but in MS-PCOS patients compared to the control group, the mutant gene was determined more.

**Key words:** folliculogenesis, heterozygotes, mutant gene, polymorphism, insulin resistance, hyperplaktinemia, hyperandrogenism, biochemical parameters.

Polycystic ovary syndrome (PCOS) is a heterogeneous syndrome characterized by hypersecretion of luteinizing hormone (LH), ovarian hyperandrogenism, polycystic ovaries, hyperinsulinemia due to insulin resistance, and reduced fertility. The variable phenotypic expression of reproductive and metabolic abnormalities in PCOS patients results in differences in oocyte developmental capacity, defined as the ability of oocytes to complete meiosis and undergo fertilization, embryogenesis, and term development. Some women with PCOS who undergo ovarian stimulation for in vitro fertilization (IVF) have normal embryonic development and a normal pregnancy outcome, while others have impaired oocyte development. Women with PCOS who are also overweight are particularly vulnerable and suffer from low egg fertilization and the inability to implant embryos in their own or other women's uterus [1,2,3,4,5].

PCOS is characterized by endocrinological disorders; therefore, polymorphisms in genes encoding sex hormones or regulators of their activity were studied [6,7,8]. The follicle-stimulating hormone receptor (FSHR) gene contains two important single nucleotide polymorphisms (SNPs) in exon 10 that are in linkage disequilibrium and replace two amino acids at positions A307T and N680S. A307T, located in the extracellular domain of FSHR, a site responsible for high-affinity hormone binding [9,10], has been reported to affect hormone transport and signal transduction. Phosphorylation of Ser and Thr residues in intracellular regions of FSHR can influence uncoupling from adenylate cyclase. As a result, the amino acid change associated with the respective SNPs can affect post-translational modifications of the FSHR protein, hence receptor function, including FSH efficiency [11,13]. Several genetic studies have examined the association between FSHR gene polymorphisms and PCOS.

Several studies have investigated whether polymorphisms of enzymes involved in the biosynthesis and metabolism of sex steroids affect the predisposition to PCOS [10]. A polymorphism was found in the regulatory region of the 17α-hydroxylase (CYP17) gene, which is a replacement of T with C -34 base pairs (bp) from the translation initiation point in the 5'-promoter region of the gene, which creates a new Msp A1 restriction site. The less common «C» allele also results in an additional promoter site like Sp1 (CCACC box), which is expected to increase gene transcription and thus lead to higher androgen levels. Although this base pair substitution is not the primary genetic defect in PCOS, it can exacerbate the clinical picture of hyperandrogenemia, especially in the presence of homozygosity [12]. On the other hand, in one of the previous studies, the CYP17 gene was not associated with the synthesis of steroid hormones in PCOS [13]. Several genetic risk factors for PCOS have been studied [9]. The CYP1A1 gene, located in the 15q22–q24 region, consists of seven exons and six introns. A polymorphism in the CYP1A1 gene encoding the cytochrome P450 1A1 enzyme has been shown to be associated with PCOS. In addition, studies have shown that the pentanucleotide repeat in the gene is associated with predisposition to PCOS [11].

In terms of CYP17A1 T/C polymorphism, proportionally, individuals carrying AG+GG gene variants were more frequently observed in patients than in controls. However, genotype and allele frequencies did not differ between cases and controls ($P > 0.05$). The frequency of the GG CYP17A1 genotype was higher among the main group compared to PCOS with metabolic syndrome. On the other hand, the frequency of the CYP17A1 AG genotype in PCOS patients was higher than in controls. CYP17A1 _ GG genotypes were found in 15% of the main, 11.6% in PCOS women with metabolic syndrome, 19% in PCOS women without metabolic syndrome, 14.4% in the control group. Although there was no statistically significant difference in the distribution of genotypes and alleles between cases and controls in terms of CYP17A1 polymorphism ($P > 0.05$), a high frequency of GG homozygous genotypes was observed in both groups [12].

**Purpose.** To achieve prognostic criteria for the outcomes of ART programs in women with infertility in PCOS based on molecular genetic predictors of folliculogenesis disorders.

**Material and methods.** Based on the foregoing, we presented the data of our own studies on the assessment, ultrasound of the pelvic organs (folliculometry with AFA calculation), hormonal studies (AMH, E, FSH, LH,

testosterone), steroid hormone genes (CYP191-57A2, rs74 ) based on the analysis of laboratory parameters.

To solve the tasks set in the work, 125 women were examined: group 1 - 45 women with primary PCOS and infertility; group 2 - 46 women with infertility and PCOS in preparation for ART; group 3 26 conditionally healthy women.

**Results.** In all 106 patients of the observed main group, a genetic study of polymorphism of the CYP17A1(rs743572) and CYP19A1(rs2470152) genes was performed. The control group consisted of 52 healthy volunteers who had no history of predisposition to PCOS. Along with this, 106 patients were also divided into 2 groups. One of them included patients with metabolic syndrome (n=60) (MS+), the second group included patients with PCOS without metabolic syndrome (n=46) (MS-). In patients with PCOS, AA homozygous or wild type of the allelic genotype of the CYP17A1 gene was 36.8%, AG heterozygous genotype in 48.1% of patients, GG homozygous mutant genotype was found in 15.1% of patients.

In our study, polymorphism of the homozygous normal or wild AA genotype of the CYP17A1 gene was observed in 45.0% of patients with MS+, compared with the MS-group where this percentage was 26.1%, in the third observation group this percentage was 40.4%. In addition, among MS+ patients with PCOS, the rate of mutant homozygous GG genotype of the CYP17A1 gene polymorphism was low and amounted to 11.7% in the first group, 19.6% in the second group and 13.5% in the control group. Also, the difference in the occurrence of the heterozygous genotype (AG genotype) in the first and second groups was 9%, and patients of the second group (54.3%) prevailed in this indicator, the difference between the indicators of the first and control groups was only 3.2%, where first group.

According to the level of occurrence of allelic variants of the CYP17A1 gene, the percentage of patients with allelic A in the MS + group was 66.7% and 55.3% in patients with the MS group. G allele was determined in 40% of patients of the first group and 43% of patients of the second group (Table 1). When we compared the level of occurrence of CYP17A1 gene polymorphism with the control group, it was found that normal - “wild” AA genotypes with a smaller difference were more common in the control group, while heterozygous AA and mutant GG genotypes slightly prevailed in the group of patients with PCOS (OR=1.06; 95%CI 0.55-2.10; p<0.8 for heterozygous genotype and OR=1.14; 95%CI 0.44-2.98; P<0.8 for homozygous genotype) (Table 1).

**Table 1**

**Results of comparison of CYP17A1 gene polymorphism between patients with PCOS and healthy people**

| Alleles and genotypes | Number of examined alleles and genotypes | | | | Хи2 | P | RR | 95%CI | OR | 95%CI |
|---|---|---|---|---|---|---|---|---|---|---|
| | Main group (n=106) | | Control group (n=52) | | | | | | | |
| | N | % | N | % | | | | | | |
| A | 129 | 60,8 | 66 | 63,0 | 0,2 | p<0,7 | 0,96 | 0,82-1,128 | 0,9 | 0,551-1,45 |
| G | 83 | 39,2 | 38 | 37,0 | 0,2 | p<0,7 | 1,0 | 0,88-1,213 | 1,1 | 0,68 - 1,815 |
| A/A | 39 | 36,8 | 21 | 40,4 | 0,2 | p<0,7 | 0,9 | 0,75-1,196 | 0,86 | 0,435 - 1,69 |
| A/G | 51 | 48,1 | 24 | 46,1 | 0,05 | p<0,8 | 1,06 | 0,85-1,328 | 1,1 | 0,55 – 2,10 |
| G /G | 16 | 15,1 | 7 | 13,5 | 0,075 | p<0,8 | 1,04 | 0,77-1,40 | 1,14 | 0,44 - 2,98 |

Interestingly, when we divided patients with PCOS into two groups with the presence of metabolic syndrome disease, we found that in the MC+ group, the wild variant (AA genotype) of the CYP17A1 gene was even higher than in the control group (45.0% and 40.4% respectively), the heterozygous variant (genotype AG) is almost equal (43.3 and 46.1%, respectively), and the mutant variant was more common in the control group. Therefore, we concluded that the importance of developing PCOS in MS+ patients with the mutant form of the genotype - GG does not matter (chi2=0.08; OR=0.85; 95% CI: 0.27 - 2.60; p=0, 77). (Table 2).

**Table 2**

**The results of genotyping of CYP17A1 gene polymorphism in patients with PCOS MS+, as well as in healthy people are presented**

| Alleles and genotypes | Number of examined alleles and genotypes | | | | Хи2 | P | RR | 95%CI | ORN | CI% |
|---|---|---|---|---|---|---|---|---|---|---|
| | PCOS with metabolic syndrome (n=60) | | Control group (n=52) | | | | | | | |
| | N | % | N | % | | | | | | |
| A | 80 | 66,7 | 66 | 63,0 | 0,25 | p = 0,61 | 1,06 | 0,88-1,38 | 1,15 | 0,66 - 1,99 |
| G | 40 | 33,3 | 38 | 37,0 | 0,25 | p = 0,61 | 0,9 | 0,72 - 1,21 | 0,87 | 0,50 - 1,50 |
| A/ A | 27 | 45,0 | 21 | 40,4 | 0,24 | p = 0,62 | 1,1 | 0,77 – 1,54 | 1,2 | 0,57 - 2,56 |
| A/G | 26 | 43,3 | 24 | 46,1 | 0,09 | p = 0,76 | 0,95 | 0,67 – 1,34 | 0,9 | 0,42 - 1,88 |
| G /G | 7 | 11,7 | 7 | 13,5 | 0,08 | p = 0,77 | 0,9 | 0,53 - 1,61 | 0,85 | 0,27 - 2,60 |

However, in the second group of patients (MC-) of the mutant form of the genotype (GG - 19.6%), as well as the heterozygous variant (AG - 54.3%) significantly prevailed in comparison with the control group (in the control group, these figures were 13.5% and 46.1%, respectively) in the control group, the homozygous AA genotype prevailed with 40.4%. Despite the fact that the value of the mutant form (GG-genotype-) developed PCOS in patients with MS- (OR=1.56) was found, it was considered unreliable (x and 2 = 0.66; 95% CI: 0.53 - 4.60; p < 0.5.) (Table 3).

**Table 3**

**Results of a study of genotyping of CYP17 gene polymorphism in MS-patients with PCOS and healthy people**

| Alleles and genotypes | Number of examined alleles and genotypes | | | | Хи2 | P | RR | 95%CI | ORN | 95%CI% |
|---|---|---|---|---|---|---|---|---|---|---|
| | PCOS with metabolic syndrome (n=46) | | Control group (n=52) | | | | | | | |
| | N | % | N | % | | | | | | |
| A | 49 | 53,3 | 66 | 63,0 | 2,1 | p < 0,2 | 0,8 | 0,59 - 1,07 | 0,65 | 0,37 - 1,16 |
| G | 43 | 46,7 | 38 | 37,0 | 2,1 | p < 0,2 | 1,25 | 0,93 - 1,67 | 1,5 | 0,86 - 2,70 |
| A/ A | 12 | 26,1 | 21 | 40,4 | 2,2 | p < 0,2 | 0,69 | 0,41 - 1,15 | 0,5 | 0,22 - 1,23 |
| A/G | 25 | 54,3 | 24 | 46,1 | 0,65 | p < 0,45 | 1,2 | 0,78 - 1,8 | 1,39 | 0,62 - 3,07 |
| G /G | 9 | 19,6 | 7 | 13,5 | 0,66 | p < 0,5 | 1,25 | 0,76 – 2,04 | 1,56 | 0,53 - 4,60 |

As a result of evaluating the efficiency of predicting polymorphism (AUC) of the CYP17A1 rs743572 gene, statistically significant indicators such as sensitivity (SE) and specificity (SP) were determined as independent markers (see Table 5). In patients of the main group, the efficiency of predicting the rs743572 mutant allele A of the CYP17A1 gene was AUC=0.51 (SE=0.63; SP=0.39; OR=1.09; 95% CI=0.75-1.59; p =0.48). Sensitivity, specificity and predictive performance of wild alleles are as follows in the group of patients with PCOS who do not suffer from metabolic syndrome: AUC=0.55; SE=0.63; SP=0.47; OR=1.49; 95% CI=0.91-2.44; p=0.64. In the group with metabolic syndrome, respectively, AUC=0.48; SE=0.63; SP=0.33; OR=0.85; 95% CI=0.53-1.37; p=0.66 (AUC

is assessed with the following criterion: AUC=0.9-1.0 - excellent quality; AUC=0.8-0.9 - high quality; AUC=0.7-0.8 - good quality ; AUC=0.6-0.7 - average quality; AUC=0.5-0.6 - poor (unsatisfactory) quality) (Table 5).

**Table 5**

**The results of evaluating the effectiveness of predicting the G allele of polymorphism of the CYP17A1 gene rs743572 in the pathogenesis of PCOS**

| Factor | Group | SE | SP | AUC | OR | 95%CI | P |
|---|---|---|---|---|---|---|---|
| G | Main group// Control group | 0,63 | 0,39 | 0,51 | 1,09 | 0,75 - 1,59 | 0,48 |
| | PCOS with metabolic syndrome// Control group | 0,63 | 0,33 | 0,48 | 0,85 | 0,53 - 1,37 | 0,66 |
| | PCOS without metabolic syndrome// Control group | 0,63 | 0,47 | 0,55 | 1,49 | 0,91 - 2,44 | 0,64 |
| | PCOS with metabolic syndrome//PCOS without metabolic syndrome | 0,53 | 0,33 | 0,43 | 0,57 | 0,33 - 0,99 | 0,52 |

When studying the prognostic efficiency of the CYP17A1 gene in the mutant genotype in the main group, MS+ and MS-groups, AUC=0.51; SE=0.15; SP=0.86; 95% CI - 0.52-2.11; p=0.5 and AUC=0.49; SE=0.12; SP=0.86; 95% CI - 0.29-2.07; p=0.37 also AUC=0.53; SE=0.2; SP=0.86; 95% CI - 0.58-3.55; p=0.29, respectively. (table 6). Predictive performance was not found to be reliable for the mutant genotype and mutant allele. Because in all groups the AUC was less than 0.6.

**Table 6**

**The results of evaluating the effectiveness of predicting the rs743572 polymorphism of the CYP17A1 gene in the pathogenesis of PCOS for the homozygous AA genotype**

| Factor | Group | SE | SP | AUC | OR | 95%CI | P |
|---|---|---|---|---|---|---|---|
| G | Main group// Control group | 0,15 | 0,86 | 0,51 | 1,05 | 0,52 - 2,11 | 0,5 |
| | PCOS with metabolic syndrome// Control group | 0,12 | 0,86 | 0,49 | 0,78 | 0,29 - 2,07 | 0,37 |
| | PCOS without metabolic syndrome// Control group | 0,2 | 0,86 | 0,53 | 1,44 | 0,58 - 3,55 | 0,29 |
| | PCOS with metabolic syndrome//PCOS without metabolic syndrome | 0,12 | 0,8 | 0,46 | 0,54 | 0,18 - 1,58 | 0,59 |

**Conclusion.** In conclusion, based on the study of CY17A1 polymorphism in patients with PCOS, it can be said that the GG mutant genotype was statistically significantly more common in patients compared to the control group. When dividing PCOS patients, they were divided into groups and compared with the control group, MS+ PCOS patients had a lower level of the mutant form (GG) genotype compared to the control group, but in MS-PCOS patients compared to the control group, the mutant gene was determined more. From this it follows that in the development of PCOS in MS-patients, the CYP17A1 gene mutation (rs743572) plays a certain role, while in MS+ patients the development of PCOS is due to factors other than the mutation of the CYP17 gene. But this finding was not significant when measured through xi2, since our results for chi2 were less than 3.84. The normal wild variant played a protective role in the main group (OR=0.9), especially in MC(-) patients (OR=0.65). When it comes to the Hardy Weinberg equation, we found no significant difference between expected and observed outcomes in the main and control group. Estimates of polymorphism prediction efficiency, as already mentioned, showed only 0.6, which means that the prediction efficiency was not reliable in terms of mutant allele and genotype.

With this, we can conclude that the mutant form (AA) of the CYP17A1 rs743572 gene is a risk of PCOS in patients without metabolic syndrome, but this risk is not significant. Our result may be supported by another study:

According to Pusalkar M. and colleagues, a CYP17A1 gene polymorphism has been associated with hyperandrogenemia. (Pusalkar, M.; Meherji, P.; Gokral, J.; Chinnaraj, S.; Maitra, A. CYP11A1 and CYP17 promoter polymorphisms associate with hyperandrogenemia in polycystic ovary syndrome. Fertil. Steril. 2009, 92, 653–659. ). Rahimi and colleagues also concluded that CYP17A1 polymorphisms are associated with the risk of PCOS.

The mechanism of hyperandrogenemia in terms of the CYP17 polymorphic variant is that the CYp19 mutant variant overexpresses alpha-hydroxylase, which leads to the production of more androgens from hydroxyprogesterone compared to the wild-type variant. Hyperandrogenism in its turn leads to disruption of normal folliculogenesis and, therefore, initiates the appearance of insulin resistance and polycystic ovaries. But in our study, we could not confirm that the polymorphic variant initiated insulin resistance, because in our metabolic syndrome group, the frequency of the CYP17 polymorphic variant was lower compared even with the control group.

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