CYP1A2 PHARMACOGENETIC MARKERS AS CLINICAL PREGNANCY PREDICTORS IN THE IN VITRO FERTILIZATION PROGRAMS FOR ANOVULATORY INFERTILITY

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Anovulatory infertility remains a significant medical and social issue requiring the development of new approaches to personalized patient management in assisted reproductive technology programs. Pharmacogenetic testing of hormone metabolism gene polymorphisms can contribute to optimization of ovarian stimulation protocols and higher in vitro fertilization (IVF) efficacy. The study aimed to assess a possible association of polymorphic variants of CYP isoenzyme genes (*CYP1A1, CYP1A2*, *CYP17A1*, *CYP19A1*) with the IVF program clinical efficacy in patients with anovulatory infertility. A total of 18 polymorphisms of the *CYP1A1*, *CYP1A2*, *CYP17A1*, and *CYP19A1* genes were analyzed by genotyping on the Illumina iScan platform. The *CYP1A2* T/T rs2470890 and A/A rs762551 genotype carrier state is associated with the increased likelihood of getting pregnant (OR = 3.824; 95% CI: 1.150–12.713, $p = 0.023$ and OR = 4.030; 95% CI: 1.372–11.839, $p = 0.009$, respectively). As for other studied polymoprhisms, including rs1048943, rs1800031, rs4646903, rs2606345 (gene *CYP1A1*), rs2069514 (gene *CYP1A2*), rs743572, rs104894136 (gene *CYP17A1*), rs10046, rs936306, rs700518, rs749292, rs1062033, rs2470152, rs28757157, rs6493497, rs7176005 (*CYP19A1*), no significant differences in the abundance of genotypes between comparison groups were revealed ($p > 0.05$). The pilot study data obtained suggest the potential role of the *CYP1A2* gene rs2470890 and rs762551 variants in modulation of the individual response to treatment and the IVF program efficacy in patients with anovulatory infertility.

Keywords: anovulatory infertility, in vitro fertilization, cytochrome P450, pharmacogenetics, *CYP1A2*, rs2470890, rs762551

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Compliance with ethical standards: the study was approved by the ethics committee of the National Research Ogarev Mordovia State University (protocol no. 116 dated 12 May 2023). All the subject submitted the informed consent to take part in the study.

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ФАРМАКОГЕНЕТИЧЕСКИЕ МАРКЕРЫ *CYP1A2* КАК ПРЕДИКТОРЫ КЛИНИЧЕСКОЙ БЕРЕМЕННОСТИ В ПРОГРАММАХ ЭКСТРАКОРПОРАЛЬНОГО ОПЛОДОТВОРЕНИЯ ПРИ АНОВУЛЯТОРНОМ БЕСПЛОДИИ

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Ановуляторное бесплодие остается значительной медико-социальной проблемой, требующей разработки новых подходов к персонализированному ведению пациентов в программах вспомогательных репродуктивных технологий. Фармакогенетическое тестирование полиморфизмов генов метаболизма гормонов может способствовать оптимизации протоколов овариальной стимуляции и повышению эффективности экстракорпорального оплодотворения (ЭКО). Целью исследования было оценить возможную ассоциацию между полиморфными вариантами генов изоферментов CYP (*CYP1A1*, *CYP1A2*, *CYP17A1*, *CYP19A1*) и клинической эффективностью программ ЭКО у пациенток с ановуляторным бесплодием. Проведен анализ 18 полиморфизмов генов *CYP1A1*, *CYP1A2*, *CYP17A1* и *CYP19A1* с использованием генотипирования на платформе Illumina iScan. Носительство генотипов T/T rs2470890 и A/A rs762551 гена *CYP1A2* ассоциировано с увеличением вероятности наступления беременности (OR = 3,824; 95% CI: 1,150–12,713, $p = 0{,}023$ и OR = 4,030; 95% CI: 1,372–11,839, $p = 0{,}009$ соответственно). Для остальных исследованных полиморфизмов, включая rs1048943, rs1800031, rs4646903, rs2606345 (ген *CYP1A1*), rs2069514 (ген *CYP1A2*), rs743572, rs104894136 (ген *CYP17A1*), rs10046, rs936306, rs700518, rs749292, rs1062033, rs2470152, rs28757157, rs6493497, rs7176005 (*CYP19A1*), статистически достоверных различий в частоте встречаемости генотипов между группами сравнения выявлено не было ($p > 0{,}05$). Полученные данные пилотного исследования указывают на потенциальную роль генетических вариантов гена *CYP1A2* rs2470890 и rs762551 в модуляции индивидуального ответа на терапию и эффективности программ ЭКО у пациенток с ановуляторным бесплодием.

Ключевые слова: ановуляторное бесплодие, экстракорпоральное оплодотворение, цитохром P450, фармакогенетика, *CYP1A2*, rs2470890, rs762551

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Anovulatory infertility representing a reproductive dysfunction resulting from the lack of ovulation occupies one of the leading positions in the structure of female infertility. Its relevance is due to not only high prevalence (which is 25–30% of all female infertility cases according to the data provided by different authors), but also complex pathogenesis, diversity of clinical forms and pronounced effects on the patient's overall health that are far beyond the reproductive dysfunction [1].

The disorder pathogenesis is multilevel and polyetiological. Regardless of the primary lesion severity (hypothalamus, pituitary gland, ovaries, or peripheral endocrine glands), the pathological cascade finally results in the deep disintegration of the hypothalamic-pituitary-ovarian axis leading to the impaired dominant follicle growth, dominance, and rupture. The basis is dysregulation of the gonadotropin-releasing hormone (GnRH) secretion circadian rhythm, which entails impaired synthesis and pulsatile secretion of the follicle-stimulating hormone (FSH) and luteinizing hormone and, therefore, blocked folliculogenesis and ovulation [1, 2].

Etiotropic therapy for anovulatory infertility is aimed at restoring the ovulatory function of the ovaries by the hormonal stimulation classified into indirect (anti-estrogen) and direct (gonadotropic) based on the application point. However, despite the existence of effective controlled ovarian stimulation protocols, there are still serious problems related to not only treatment resistance, high risk of complications, such as ovarian hyperstimulation syndrome and multiple pregnancy, but also psychological discomfort in the patient and her partner due to the treatment protocol duration and cyclical nature [3–5].

The today's reproductive medicine pays considerable attention to the search for genetic markers allowing one to predict the response to ovulation stimulation and the IVF program efficacy. In the context of anovulatory infertility, genetic studies are focused on polymorphisms of the genes involved in regulation of folliculogenesis, steroidogenesis, insulin metabolism, and gonadotropin sensitivity [6–8].

Biotransformation of a significant number of endogenous steroids, xenobiotics, and drugs is mediated by the cytochrome P450 (CYP) family enzymes classified as heme-based monooxygenases [9]. In the reproductive function regulation process, a special role is given to the CYP isoforms that are localized in the steroid-producing tissues: adrenal cortex, ovaries, and placenta. The main function of estradiol 2-hydroxylation in the liver is implemented by the CYP1A2 isoform, while in the extrahepatic tissues similar catalytic activity is shown by CYP1A1 [10–12]. CYP17A1 (17α-hydroxylase/17,20-lyase) is the key enzyme catalyzing two successive phases: 17-α-hydroxylation of progesterone and pregnenolone and the side chain cleavage (17,20-lyase activity) yielding androgens (dehydroepiandrosterone and androstenedione). CYP19A1 (aromatase) catalyzes the conversion of androgens (testosterone and androstenedione) into estrogens (estradiol and estrone) [13]. Abnormal functioning of specific isoforms leads to profound steroidogenesis dysfunction manifested by either deficiency of estrogens necessary for ovulation, or excess androgens, which block the follicle growth and maturation.

High CYP enzyme genetic polymorphism rate results in a broad spectrum of enzyme activity alterations, which have a significant effect on the xenobiotic metabolism, risk of side effects and regulation of physiological processes [14, 15]. The authors had earlier identified the associations of some CYP polymorphisms allowing one to predict the response to ovulation stimulation and the IVF efficacy [16, 17].

The study aimed to assess a possible association of polymorphic variants of the CYP isoenzyme genes (*CYP1A1*, *CYP1A2*, *CYP17A1*, *CYP19A1*) with the IVF program clinical efficacy in patients with anovulatory infertility.

METHODS

The study involved 176 females diagnosed with anovulatory infertility (ICD-10 code N97) in accordance with the criteria of European and Russian clinical guidelines. These patients requested an IVF program at the assisted reproductive technology department of the Perinatal Center, Mordovian Republican Central Clinical Hospital (Saransk), between May 2023 and December 2024. All the study participants were in their early fertile age, 25–35 years (29.4 ± 3.7 years); they were of Caucasian origin, were born and lived in the Volga Federal District of Russia. All the patients were through the IVF program, involving the use of their own oocytes and embryo transfer; the program involved the use of the GnRH antagonists (subcutaneous ganirelix, cetrorelix 0.25 mg/day), recombinant gonadotropins (subcutaneous follitropin alfa, starting dose 150–225 IU/day with subsequent adjustment), and choriogonadotropin alfa (subcutaneous ovitrelle 250 μg) within the framework of the short superovulation stimulation protocol. The prescribed assessment and treatment were conducted in accordance with the National clinical guidelines on treatment of female infertility and assisted reproductive technology/intrauterine insemination.

A total of 60 women were selected for enrollment based on the inclusion criteria. Inclusion criteria: women aged 25–35 years; infertility due to the lack of ovulation; normal ovarian reserve; no endometrial abnormality based on the ultrasonography, hysteroscopy data; normal karyotype in both partners. Exclusion criteria: extragenital and genital abnormalities, due to which there were contraindications for the basic IVF program; patient's voluntary refusal to take part in the study at any stage.

The fact of getting pregnant (pregnancy was diagnosed by determining serum concentrations of the human chorionic gonadotropin β-subunit 14 days after the embryo transfer to the uterine cavity) was considered as a major outcome in the women assessed; the test was considered to be positive, when the levels were above 30 IU/L (biochemical pregnancy). Ultrasonographic diagnosis of clinical pregnancy to determine the number of fertilized eggs in the uterine cavity was performed 21 days after the embryo transfer. On day 31, physicians of appropriate specialty performed ultrasonography in order to detect fetal heartbeat. Women were divided into groups based on the major IVF program outcome considering their enthicity, demographic and medical history data: group 1 (index group) consisted of women, who got pregnant after one try and had no history of IVF attempts ($n = 30$); group 2 (comparison group), who failed to get pregnant and had a history of three unsiccessful IVF attempts ($n = 30$).

On the day of enrollment, each patient underwent additional venous blood collection: 6 mL of blood were collected by venipuncture from the cubital vein in the morning in the fasting state into the disposable sterile EDTA vacuum tube for further genotyping. Biomaterial was frozen at a temperature of –20 °C, transported to the laboratory, and then stored at –70 °C. DNA was isolated from blood using a magnetic sorbent and reagents by Genotek (Russia) in the Allsheng Auto-Pure 96 system (China). When performing the whole-genome testing, sample preparation and scanning were accomplished using the iScan system (Illumina, USA) in accordance with the Infinium HTS Assay Guide protocol [18]. The Infinium Global Screening Array-24 v3.0 kit was used (USA). In this study a total of

18 single nucleotide polymorphisms (SNPs) were analyzed, which, in the authors' opinion developed based on the literature review, could have predictive potential: rs1048943, rs1800031, rs2606345, rs4646903 (*CYP1A1*), rs762551, rs2069514, rs2470890 (*CYP1A2*), rs743572, rs104894136 (*CYP17A1*), rs10046, rs936306, rs700518, rs749292, rs1062033, rs2470152, rs28757157, rs6493497, rs7176005 (*CYP19A1*).

Statistical data processing was performed using the StatSoft Statistica 12.5 software package. The quantitative trait distribution was tested for normality using the Shapiro–Wilk test. The normally distributed quantitative indicators were presented as the mean and standard deviation (M (±SD). Comparison of two independent groups based on quantitative traits was performed using the Student's *t*-test. Qualitative traits (genotype and allele frequencies) were compared using the Pearson's chi-squared test (χ^2) or Fischer's exact test (when the expected frequencies in the contingency table cells were below 5). The genotype distribution consistency with the Hardy–Weinberg principle (HWE) was tested in the control group using the χ^2 test. The strength of associations between genotypes and the IVF program outcomes was assessed by calculating the odds ratio (OR) and 95% confidence interval (95% CI). When testing statistical hypotheses, the critical significance level (p) was set at 0.05. Considering the limited sample size ($n = 60$) and the need to exclude false positives typical for asymptotic tests (chi-squared test), significance of the associations revealed was verified using the permutation test. The Monte Carlo permutation test involving generation of 10,000 random phenotype permutations with the preserved genotype-based structure of the sample was used. This approach is considered to be a gold standard of genetic testing in small samples, since it does not depend on the data distribution pattern and allows one to accurately calculate the error probability empirical value (p-perm). The empirical levels $p < 0.05$ were considered significant.

RESULTS

The groups were matched for age, infertility duration, fact of having obesity, basal FSH and estradiol levels, anti-Müllerian hormone (AMH) levels, and the number of antral follicles ($p > 0.05$) (Table 1). We believe that the differences in the response to ovulation stimulation and IVF efficacy can be due to genetic differences in *CYP1A1*, *CYP1A2*, *CYP17A1*, *CYP19A1*.

Comparative analysis of the distribution of frequencies of genotypes with polymorphisms of these genes in the groups of patients with beneficial and adverse IVF outcomes revealed polymorphic variants significantly correlated to the successful implantation and the fact of getting pregnant (Table 2). The distribution of genotypes in the control group was compliant with the Hardy–Weinberg equilibrium ($p > 0.05$)

Thus, in the *CYP1A2* gene, the rs2470890 polymorphism T/T genotype carrier state is associated with the 3.8-fold increased likelihood of successful IVF (OR = 3.824; 95% CI: 1.150–12.713, $p = 0.023$). In contrast, the C/C genotype was far less abundant in the group with beneficial outcomes, representing the risk factor of unsuccessful attempts (OR = 0.167; 95% CI: 0.033–0.853, $p = 0.016$). We also determined a significant association between the *CYP1A2* rs762551 polymorphism A/A genotype and positive IVF outcomes: the genotype carrier state increases the likelihood of getting pregnant 4-fold (OR = 4.030; 95% CI: 1.372–11.839, $p = 0.009$) relative to the carrier state for other genotypes. At the same time, the C/C genotype of this locus showed a downward trend of frequency in the group with beneficial outcomes (OR = 0.167; 95% CI: 0.033–0.853, $p = 0.016$), which can indicate its unfavorable prognostic value.

As for other studied polymorphisms, including rs1048943, rs4646903, rs2606345 (gene *CYP1A1*), rs2069514 (gene *CYP1A2*), rs743572 (gene *CYP17A1*), and a number of loci of the gene *CYP19A1* (rs936306, rs28757157, rs749292, rs10046, rs700518, rs1062033, rs2470152, rs6493497, rs7176005), no significant differences in the abundance of genotypes between comparison groups were revealed ($p > 0.05$). As for polymorphisms rs1800031 (gene *CYP1A1*) and rs104894136 (gene *CYP17A1*), associations could not be analyzed due to the sample monomorphism.

Primary analysis involving the use of standard parametric tests revealed significant differences in the distribution of genotypes across the *CYP1A2* loci. To confirm the fact that the results were resistant to the small sample effect, a permutation test was performed. For the rs762551 polymorphism (genotype A/A), the empirical significance value obtained based on the 10,000 resampling, confirmed the non-random nature of the association (p-perm = 0.012, OR = 4.03). A similar result was reported for the rs2470890 polymorphism (genotype T/T): the empirical p-value also retained statistical significance (p-perm = 0.025, OR = 3.82). Thus, the use of permutation analysis confirmed the fact that high likelihood of getting pregnant in carriers of these genotypes is not a statistical "artifact" associated with the sample size, but reflects a real biological pattern.

DISCUSSION

In this study, to assess possible associations of polymorphic variants of the cytochrome P450 isoenzyme-encoding genes (*CYP1A1*, *CYP1A2*, *CYP17A1*, *CYP19A1*) with the IVF program clinical efficacy in patients with anovulatory infertility, the analysis of the distribution of frequencies of 18 SNP genotypes was conducted. The data obtained suggest that two polymorphisms are associated with beneficial IVF program outcomes: rs2470890 and rs762551.

The two SNPs located in the intronic region of the gene *CYP1A2* encoding the enzyme that is responsible for 2-hydroxylation of estradiol in the liver can alter the activity of CYP1A2, which affects the estrogen metabolism, thereby affecting the women's responsiveness to ovarian stimulation in IVF programs. The rs2470890 and rs762551 association with the CYP1A2 protein expression was illustrated by other estrogen-dependent conditions [12, 19]. The A allele of the rs762551 polymorphism (*CYP1A2*) is associated with the increased enzyme inducibility and, therefore, with the higher rate of the estrogen and xenobiotic metabolism [20].

At first glance, the accelerated estradiol metabolism can be considered as a negative factor reducing the hormone levels. However, in the context of controlled ovarian stimulation, during which estradiol levels often reach supraphysiological values, high CYP1A2 activity can play a protective role. We assume that the effective estrogen biotransformation reported in carriers of the rs762551 (A/A) and rs2470890 (T/T) genotypes prevents the endometrium overexposure to high doses of exogenous and endogenous hormones. There is evidence that excess estradiol can reduce endometrial receptivity and disrupt synchronizarion of the embryo development and endometrial readiness, thereby shifting the "implantation window" [21–23].

The controlled ovarian stimulation protocol that precedes IVF is based on administration of supraphysiological exogenous gonadotropin doses aimed at inducing multiple folliculogenesis. Multifollicular development results in hypersecretion of estradiol,

Table 1. Major diagnostic criteria of the surveyed women's ovulatory potential

Indicators	Group 1 (*n* = 30)	Group 2 (*n* = 30)	χ^2	*p*
Age				
25–30	43.3% (13 individuals)	50% (15 individuals)	0,268	0.605
31–35	56.7% (17 individuals)	50% (15 individuals)		
Obesity				
Yes	23.3% (7 individuals)	40% (12 individuals)	1,926	0.166
No	76.7% (23 individuals)	60% (18 individuals)		
AMH				
Below 1.0 ng/mL	13.3% (4 individuals)	40% (9 individuals)	–	0.114*
1.0–3.5 ng/mL	73.4% (22 individuals)	60% (18 individuals)	1,274	0.274
Over 3.5 ng/mL	13.3% (4 individuals)	10% (3 individuals)	–	0.688*
Basal FSH				
Below 10 IU/L	50% (15 individuals)	43,3% (13 individuals)	0,268	0.605
Over 10 IU/L	50% (15 individuals)	56,7% (17 individuals)		
Basal estradiol				
Below 40 pg/mL	63.3% (19 individuals)	70% (21 individuals)	0,300	0.584
Over 40 pg/mL	36.7% (11 individuals)	30% (9 individuals)		
Antral follicle counts				
Below 5	–	10% (3 individuals)	–	–**
5–12	80% (24 individuals)	80% (24 individuals)	0	1000
Over 12	20% (6 individuals)	10% (3 individuals)	–	0.275*

Note: * — *p* is compliant with Fischer's exact test; ** — not calculated due to the lack of cases in one of the groups.

the levels of which are significantly higher than the natural ovarian cycle indicators. The resulting excessive steroid load has a modulatory effect on the endometrial maturation, causing the "implantation window" shift. The phenomenon pathogenesis is based on the complex of structural, transcriptional, and immunoregulatory changes in the endometrium, which eventually determines its receptive status [22].

At the molecular level, supraphysiological estradiol concentrations induced by ovarian stimulation has a modulatory effect on the transcriptome activity of the genes associated with endometrial receptivity. Suppression of the progesterone receptor expression accompanied by dysregulation of the genes that are cucial for successful embryo implantation, such as Cox1, Lif, Ptgs2, and Hegfl, is reported as one of the key mechanisms [24–26]. Furthermore, hyperestrogenism typical for the stimulated cycle results in suppression of expression of the Hoxa11 and Cdh1 factors, which also adversely affects the endometrium receptive properties. In parallel, the impaired spatiotemporal expression of the estrogen and progesterone receptors is observed, which suggests systemic alteration of the endocrine signaling in the endometrium under the exposure to exogenous gonadotropins [23, 27].

Thus, the genetically determined active metabolism can contribute to maintaining the hormonal balance more favorable in terms of the embryo implantation, which is in line with the clinical results we have obtained.

The lack of significant differences in the distribution of genotypes across the groups of women, who got pregnant and failed to get pregnant, for the *CYP17A1* and *CYP19A1* steroidogenesis genes can indicate that in the context of exogenous gonadotropin stimulation the one's own estrogen production variability the plays a less important role, than their systemic metabolism and CYP1A2-mediated clearance.

This study has a number of limitations. First, these are related to the small sample size (*n* = 60), which is typical for pilot projects. It is well known, that genetic testing in small groups is associated with the risk of false positives (type I error). However, the permutation testing method we have used (10,000 permutations) allows one to reliably filter out random findings. The fact that the associations of the *CYP1A2* polymorphism (rs762551 and rs2470890) were still significant when applying the permutation control, in combination with the high odds ratio (OR > 3.8), suggests reliability of the data obtained, regardless of the pilot study design limitations. Second, the impact of the concomitant therapy and other clinical factors potentially modulating the effect of the drugs used for controlled ovarian stimulation was not assessed in this study. Nevertheless, the patterns revealed (high odds ratio: OR > 3.0) suggest a significant clinical effect of the studied loci.

The data obtained justify the feasibility of further research focused on the *CYP1A2* polymorphisms as potential biomarkers for IVF protocol personalization.

CONCLUSIONS

The pilot study conducted revealed significant associations between the *CYP1A2* gene polymorphisms and IVF outcomes in women with anovulatory infertility. The data obtained suggest that the CYP1A2 rs2470890 T/T homozygous genotype and rs762551 A/A homozygous genotype carrier state is associated with the more than 3-fold increased chance of getting pregnant after IVF (OR = 3.824 and OR = 4.030, respectively). These associations that reach the statistical significance level ($p = 0.023$ and $p = 0.009$) are characterized by relatively narrow confidence intervals, which indicates sufficient reliability of the patterns revealed in the current sample.

The lack of significant differences in the distribution of genotypes across other 16 studied polymorphisms of the cytochrome P450 family genes (*CYP1A1*, *CYP17A1 и CYP19A1*) does not eliminate their potential role in regulation of the endocrine processes coupled with the controlled ovarian stimulation. It is likely that the influence of these polymorphisms

Table 2. Distribution of some polymorphisms of the CYP system genes in women with anovulatory infertility

Gene	Polymorphism	Genotypes	Group 1 (*n* = 30)	Group 2 (*n* = 30)	χ^2 (chi-squared test)	OR	95% CI	*p*
CYP1A1	rs1048943	T/T	28	28	0	–	–	1.00
		T/C	2	2		–	–	
	rs1800031	A/A	30	30	–	–	–	–
	rs4646903	A/A	25	26	–	0.769	0.185–3.198	0.718**
		A/G	5	4		1.300	0.313–5.404	
	rs2606345	A/A	16	19	0.617	0.662	0.236–1.858	0.433
		C/A	12	9	0.659	1.556	0.534–4.532	0.417
		C/C	2	2	0	–*	–	1.00
CYP1A2	rs2470890	C/C	2	9	–	0.167	0.033–0.853	0.016**
		C/T	15	16	0.067	0.875	0.318–2.410	0.797
		T/T	13	5	5.079	3.824	1.150–12.713	0.023
	rs2069514	G/G	28	29	–	–*	–	0.50**
		G/A	2	1		–*	–	
	rs762551	A/A	19	9	6.696	4.030	1.372–11.839	0.009
		C/A	9	12	0.659	0.643	0.211–1.873	0.417
		C/C	2	9	–	0.167	0.033–0.853	0.016**
CYP17A1	rs743572	G/G	6	9	0.800	0.583	0.178–1.913	0.372
		G/A	15	14	0.067	1.143	0.415–3.148	0.797
		A/A	9	7	0.341	1.408	0.445–4.453	0.560
	rs104894136	G/G	30	30	–	–	–	–
CYP19A1	rs10046	A/A	10	9	0.077	1.167	0.393–3.467	0.782
		A/G	14	14	0	–	–	1.00
		G/G	6	7	0.098	0.821	0.240–2.814	0.755
	rs936306	C/C	16	15	0.067	1.143	0.415–3.148	0.797
		T/T	4	2	–	2.154	0.363–12.764	0.386**
		T/C	10	13	0.635	0.654	0.229–1.864	0.426
	rs700518	C/C	10	9	0.077	1.167	0.393–3.467	0.782
		T/T	7	7	0	–	–	1.000
		T/C	13	14	0.067	0.874	0.316–2.418	0.796
	rs749292	A/A	6	10	1.364	0.500	0.155–1.616	0.243
		G/A	15	11	1.086	1.147	0.411–3.204	0.298
		G/G	9	9	0	–	–	1.000
	rs1062033	C/C	8	7	0.089	1.195	0.371–3.853	0.766
		G/C	13	12	0.069	1.147	0.411–3.204	0.794
		G/G	9	11	0.300	0.740	0.252–2.175	0.584
	rs2470152	A/A	8	6	0.373	1.455	0.435–4.860	0.542
		G/A	16	14	0.267	1.306	0.474–3.602	0.606
		G/G	6	10	1.364	0.500	0.155–1.616	0.243
	rs28757157	C/C	19	21	0.300	0.740	0.252–2.175	0.584
		T/T	3	3	0	–	–	1 000
		T/C	8	6	0.373	1.455	0.435–4.860	0.542
	rs6493497	G/G	21	20	0.077	1.167	0.393–3.467	0.782
		G/A	9	10		0.857	0.228–2.547	
	rs7176005	C/C	21	20	0.077	1.167	0.393–3.467	0.782
		C/T	9	10		0.857	0.228–2.547	

Note: * — not calculated due to the lack of cases in one of the groups или of the critically low number of observations; ** — *p* is compliant with Fischer's exact test.

on IVF outcomes is either of more complex nature requiring the analysis of genotype-genotype interactions, or is manifested at the level of other mechanisms not covered by simple association analysis.

The reported association of *CYP1A2* polymorphisms with the IVF success can result from the crucial role of this enzyme in metabolism of estrogens and other hormonal substrates that determine the effectiveness of ovarian stimulation. The differences in the CYP1A2 enzyme activity depending on the genotype can affect the circulating hormone levels, oocyte quality, and endometrial receptivity, being valuable predictors of the assisted reproductive technology success.

The data obtained open the prospects for the development of molecular genetic tests allowing for preliminary patient stratification based on the IVF success likelyhood. Integration of the information about *CYP1A2* genotypes into predictive models might contribute to personalization of the controlled ovarian stimulation protocols, gonadotropin dosing optimization, and improvement of the assisted reproductive technology efficacy. However, the *CYP1A2* genotyping introduction into clinical practice requires additional prospective trials, pharmacogenetic analysis, and the development of evidence-based clinical guidelines.

Thus, the study representing an important step towards understanding the fertility molecular genetic underpinnings can provide the basis for the development of innovative approaches to personalized management of patients with unovulatory infertility in the assisted reproductive technology programs.

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