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ORIGINAL ARTICLE

Toward optimal set of single nucleotide polymorphism investigation before IVF

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Abstract

Background: At present, the patient preparation for IVF needs to undergo a series of planned tests, including the genotyping of single nucleotide polymorphism (SNP) alleles of some genes. In former USSR countries, such investigation was not included in overwhelming majority of health insurance programs and paid by patient. In common, there are prerequisites to the study of more than 50 polymorphisms. An important faced task is to determine the optimal panel for SNP genotyping in terms of price/number of SNP.

Materials and methods: During 2009–2015 in the University Hospital of St. Petersburg State University, blood samples were analyzed from 550 women with different reproductive system disorders preparing for IVF and 46 healthy women in control group. In total, 28 SNP were analyzed in the genes of thrombophilia factors, folic acid cycle, detoxification system, and the renin-angiotensin system. The method used was real-time PCR.

Results: A significant increase in the frequency of pathological alleles of some polymorphisms in patients with habitual failure of IVF was shown, compared with the control group. As a result, two options defined panels for optimal typing SNP before IVF were composed. Standard panel includes 8 SNP, 5 in thromborhilic factors, and 3 in folic acid cycle genes. They are 20210 G > A of FII gene, R506Q G > A of FV gene (mutation Leiden), -675 5G > 4G of PAI-I gene, L33P T > C of ITGB3 gene, -455 G > A of FGB gene, 667 C > T of MTHFR gene, 2756 A > G of MTR gene, and 66 A > G of MTRR gene. Extended panel of 15 SNP also includes 807 C > T of ITGA2 gene, T154M C > T of GP1BA gene, second polymorphism 1298 A > C in MTHFR gene, polymorphisms of the renin-angiotensin gene AGT M235T T > C and -1166 A > C of AGTR1 gene, polymorphisms I105V A > G and A114V C > T of detoxification system gene GSTP.

Conclusion: The results of SNP genotyping can be adjusted for treatment tactics and IVF, and also medical support getting pregnant. The success rate of IVF is increased as the result, especially in the group with the usual failure of IVF.

Keywords

Detoxification, female reproduction disorders, folic acid cycle, IVF lead-up, rennin-angiothensin system, SNP, thrombophilic factors

Introduction

At present, IVF patients must undergo a series of planned tests for the procedure preparation. One of these studies is to determine the alleles of single nucleotide polymorphism (SNP) of several genes of folic acid cycle and blood clotting factors. Quite a lot of works devoted to the advantage of such genetic testing for various female reproductive system disorders [1,2].

Among the vast majority of studies on the impact of 1–2 SNP, a maximum of three polymorphisms in the predisposition to a violation of women's reproductive health, often recurrent miscarriage, highlighted the work devoted to the study of the joint effect of a plurality of SNP [3–5]. Despite the obvious advantages of such a study, particularly in cases of habitual failure of IVF, when his appointment is still a number of unresolved issues. Among these issues the most important are the number and a list of studied SNP.

On the one hand, it is desirable to explore the greatest number of SNP genes coagulation factors, gene folate cycle enzymes, renin-angiotensin system, detoxification system, transcription factors, etc. The need to study a number of SNP to determine the optimal treatment strategy has repeatedly proved, especially in conditions associated with a change in hormonal levels [6]. This need is reflected in the recommendations of the National Medical Eligibility Criteria for contraceptive methods in 2012.

On the other hand, an excessive amount of information about the status of the patient's SNP may ''confusing'' the physician in selecting the required treatment strategy. In addition, the SNP testing is not included in the compulsory health insurance, and in most cases is paid by the patient themselves. There are a number of clinical studies [7,8] of impact absence of pathological alleles number of SNP on the development of the female reproductive disorders and the effectiveness of IVF.

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The majority of commercial laboratories in the post-Soviet space as a preparation for IVF recommend holding global genetic testing including SNP profile. Manufacturers of reagents for such tests began to prepare multiplex kits directly to analyze a significant amount of SNP [9]. Therefore, the composition of an optimal panel tested SNP before IVF is an important problem of modern gynecology and biomedicine.

In the course of this study, the effect of 28 SNP for the preparation for the procedure of IVF was analyzed. It is shown that the most important clinical value is a package of 8–9 SNP of three gene groups: the most important coagulation factors FII (prothrombin) and FV (Leiden mutation), ''auxiliary'' factors of pathological alleles in genes PAI-I, ITGB3, ITGA2 and/or FGB, and SNP of folic acid cycle genes MTHFR, MTRR, and MTR. Investigation of other ''auxiliary'' clotting factors, SNP of renin-angiotensin system, and detoxification systems genes makes sense to carry out only if there are clear clinical indications and is only to confirm the appropriateness of treatment chosen.

Materials and methods

Venous blood samples of 550 women were analyzed. All of them sought medical treatment due to problems in the reproductive sphere in 2009–2015. The vast majority of them (392) were further IVF, 218 of them repeatedly (they formed a group of regular unsuccessful IVF). All studied patients belonged to the Russian population from different regions of Russia.

All patients completed the informed consent to provide biological samples for anonymous research.

The control group consisted of 46 healthy women who have at least one healthy child. The examined women were between 22 and 42 years old.

DNA purification was made out of peripheral blood leukocytes either by using the kit and protocol for DNA extraction ''DNA-express-blood'' of Litekh Research and Production Company, Moscow, Russia, in accordance with the manufacturer's recommendations (2009–2013) or by absorption on magnetic silica using reagents ''AmpliSens'' production FBUN ''Central Research Institute of Epidemiology'', Moscow, Russia and the automated installation XIRIL, XIRIL AG, Switzerland (2014–2015). Concentration of genomic DNA, obtained during the both above-mentioned processes, was 20–100 ng.

SNP analysis was performed either by using a reagent kit for allele-specific PCR of Litekh Research and Production Company, Moscow, Russia, followed by electrophoretic detection (2009–2013) as described pereviously [10] or using a reagent kit for the real-time PCR and thermocycler ''DNA-Technology Prime'' production of LLC ''DNA-Technology'', Moscow, Russia (2014–2015).

All procedures were in accordance with the test kits manufacturer's instructions.

Statistical processing of the results was carried out using Statistica 10, Microsoft Excel and ''Calculator for statistics of studies with case control'', submitted on the site of State Research Centre of the Russian Federation GENETIKA (http://www.gen-expert.ru). Statistical analysis included the combination of two samples series according to one criterion. The criterion meant the existence (absence) of a definite allele, genotype, or their combination in several genes.

Statistical analysis of accuracy of differences in distribution of the alleles and genotypes frequencies between the analyzed samples series and detection of genotype association with the disease development were performed using the standard method of Yates' chi-squared test (if $p < 0.05$ the results were considered statistically significant). In order to describe the relative risk of disease the odds ratio (OR) was calculated.

OR = 1 was considered as association absence. OR > 1 – was considered as positive association (increased risk of pathology development), OR < 1 – was considered as negative association of allele or genotype with the disease (low risk of pathology development).

Results

List of SNP analyzed and the number of patients studied are presented in Table 1.

At the beginning of the study, each woman was subjected to analysis as much as possible up to the maximum number of SNP in different groups of genes. This panel includes 15 SNP in total. Gradually the amount of studied SNP in the panel decreased due to economic considerations eventually reaching number 8.

The composition of the panel surely includes the SNP in ''basic'' blood clotting factors – FII and FV, and three gene polymorphisms of folate cycle in MTR, MTRR, and MTHFR genes. These five SNP exactly as the most proven influencing the susceptibility to the development of thrombophilic states have made the base of the research panel. The remaining number of polymorphisms studied included ''auxiliary'' SNP in thrombophilic factors of the renin-angiotensin system, detoxification system, and polymorphism V617F G > T in Janus kinase gene JAK2.

Certain frequencies of genotypes were generally in line with the average values for the European/North American population. A comparison was carried out with the data contained in the database of allele frequency data U.S. National Science Foundation, placed http://alfred.med.yale.edu/alfred/index.asp.

Below the data on specific genotype frequencies of some but not all SNP are presented.

Among surveyed 550 patients, the Leiden mutation in the heterozygous state was detected in 38 women and 1 in the homozygous state. The frequency of allele A was 3.64%. Mutation 20210 G > A in prothrombin gene was detected in the heterozygous state in 29 patients and was not found anybody with homozygous AA pathological variant. The frequency of pathological allele A was 2.64%. Extremely high frequency variation of genotypes detected in polymorphism -675 5G > 4G in plasminogen activator inhibitor gene PAI-I (Serpene1): from 502 examinees option 5G/5G detected in 178, heterozygote 5G/4G in 168 and pathological homozygote in 156 people. The frequencies of alleles 5G/4G amounted to 52.2/47.8%.

In the most important polymorphism of the folic acid cycle gene network 667 C > T of methylenetetrahydrofolate reductase gene MTHFR allele frequency was 58.7/41.3% (227 patients with CC genotype, 192 with genotype CT, 131 with pathologic homozygous genotype TT). The second significant polymorphism in the MTHFR gene 1298 A > C demonstrated the frequency of allele A and C as follows: 73.3% A/26.7% C (144 patients with genotype AA, 61 with genotype AC, 33 pathologic homozygous CC genotype). For polymorphism 2756 A > G in methionine synthase gene MTR normal homozygous AA was detected in 333 patients, heterozygous state AG in 139 people, pathological homozygous GG in 78. Statistical significance for pathologic allele G in this SNP is absent. The frequency of alleles A and G was 73.2%/26.8%, respectively. The remaining two SNP of the folate cycle genes also showed no significant clinical relevance demonstrated following allele frequencies: SNP 1598 G > A in gene metilentetragidrofolatdegidrogenase MTHFD1 G/A 84.6%/15.4% (36 normal homozygotes, 16 heterozygotes, no pathological homozygotes), SNP 80 A > G in folate transporter gene SLC19A (RFC1) A/G 81.7%/18.3% (35 normal homozygotes, 15 heterozygotes, 2 pathological homozygotes).

For SNP's in the glutathione transferase pi gene GSTP the following frequencies of alleles identified: in polymorphism

Table 1. SNP tested and the genotypes frequencies identified.

No.	Physiological group	Gene	SNP	Frequency in the population, % (database)	Frequency in the sample, %	Frequency in control, %	Number of studies (control always = 46)	OR (95% CI)
1	Thrombophilia factors	FII	20210 G > A	1.5–2.2	2.64	1.09	550	2.46
2		FV	R506Q G > A	1.5–2.2	3.64	0	550	7.07
3		PAI-I	−675 5G > 4G	30–50	47.8	31.3	502	2.09
4		ITGB3	L33P T > C	12	18	14.3	502	1.42
5		FGB	−455 G > A	7–24	29.1	22.8	398	1.16
6		ITGA2	807 C > T	15–20	42.8	29.5	430	2.36
7		GP1BA	T154M C > T	6.6–16	12	10.8	347	1.12
8		FVII	10976 G > A	5–14	7.4	8.8	126	0.89
9			−323 ins 10 bp	3–5	3.1	4.9	98	0.72
10		FXIII	V34L G > T	10–15	13	18.2	54	0.74
11		EDN1	K198N G > T	30–40	31.6	29.7	126	1.18
12		P2RY12	H1/H2	16	12.4	11.9	90	1.06
13		NOS3	894 G > T	30–40	25.8	22.0	112	1.20
14		CRP	3872 C > T	33	30	28.2	52	1.14
1	Folic acid cycle	MTR	2756 A > G	19–25	26.8	27.2	550	0.98
2		MTRR	66 A > G	39–49	58.4	42.4	550	1.9
3		MTHFR	667 C > T	32–40	41.3	18.5	550	3.1
4			1298 A > C	23–29	26.7	21.7	238	1.31
5		MTHFD1	1598 G > A	15–30	15.4	14.1	52	1.1
6		SLC19A	80 A > G	25–32	18.3	18.5	52	0.99
1	Renin-angiotensin system	AGT	T174M C > T	10–15	12	12.7	197	0.92
2			M235T T > C	34–43	38.4	27.8	197	1.44
3		AGTR1	−1166 A > C	17–30	33.3	28.5	197	1.39
4		ACE	Alu Ins/Del	45–55	52	41	98	1.18
1	Detoxification system	GSTP	I105V A > G	33.62	42.5	37.0	126	1.26
2			A114V C > T	5.12	8.7	9.8	144	0.88
3		PON1	Q192R A > G	20–30	22.6	19.4	144	1.07
1	Janus kinase	JAK2	V617F G > T	0.20	0	0	74	0.62

I105V A > G 42.5% A and 57.5% G (48 normal homozygotes, 49 heterozygotes, 29 pathological homozygotes), in polymorphism A114V C > T 91 3% C and 8.7% T (120 normal homozygotes, 23 heterozygotes, 1 pathological homozygotes).

Alleles frequency identified for SNP Q192R A > G in paraoxonase gene PON1 accounted for G/T of 77.4%/22.6% (97 normal homozygotes, 37 heterozygotes, 10 pathological homozygotes).

Among the 74 patients who were examined for the presence of mutations V617F G > T of the Janus kinase gene JAK2 pathological allele T were found none.

Discussion

As a result of the investigation the role of SNP in calculating the possible pathological primarily thrombophilic complications in preparation for IVF the panel of the 8–9 most important polymorphisms is picked. This SNP are ones in genes FII, FV, PAI-I, ITGB3, ITGA2/FGB, MTHFR, MTR, MTRR (Table 2).

Patients tested on the profile allows assign appropriate therapy in time before the thrombophilic state occurs. This statistically significantly increases the effectiveness of IVF in women with habitual failure of IVF [11,12]. Also the presence of the data about pathological alleles in this SNP panel genes allows to reduce the number of spontaneous abortions in women with recurrent miscarriage [6]. As a molecular mechanism provoking spontaneous thrombosis at the time of implantation and early placental development, we can assume the presence of explosive angiogenesis in which the development of an extensive vascular network is occurs during the extremely short period of time. It is in this state the pathological SNP alleles which are the variants of norm under ordinary conditions provoke the displacement of equilibrium in thrombolytic system leading to spontaneous thrombosis in developing vessels.

Table 2. Final SNP testing panel.

No.	Gene	SNP
1	FII	20210 G > A
2	FV	R506Q G > A
3	PAI-I	−675 5G > 4G
4	ITGB3	L33P T > C
5	ITGA2 or FGB	807 C > T −455 G > A
6	MTR	2756 A > G
7	MTRR	66 A > G
8	MTHFR	667 C > T

Another aspect for screening the genetic factors of thrombophilia is a relatively recent revealed phenomenon that ovarian stimulation provokes venous thrombosis in women later in their life [13,14].

SNP in blood coagulation factors genes which were included in the final panel

During the detailed contemplation of the results, it is plain that the undoubted importance to prepare for IVF have a SNP in the gene FII and FV. The presence of pathological alleles in these genes in the heterozygous state entails problems in female reproduction directly proportional to the age of the patient [4,6,15–18]. At the molecular level, this manifests itself in violation of the balance between prothrombin and thrombin which causes 3–8 times increased risk of thrombosis [19]. It is noted repeatedly that the risk of thrombosis in carriers of FII and FV genes mutations magnified in violation of hormonal background, such as oral contraceptives, menopause hormone correction, and hiperovulation stimulation during IVF [20,21]. Thrombophilic conditions induced, in particular, FII and FV genes mutations are a cause for ovarian hyperstimulation syndrome [22]. Wherein the

development of thrombophilic states may be minimized in advance by the therapy with preventive doses of thrombolytics, such as low molecular weight heparin, enoxaparin, or aspirin [23,24]. It is for these reasons FII and FV genes mutations are the first priority in SNP analysis panel presented.

Contrary to this point of view, there are some evidences that the presence of pathological alleles in FII and FV genes in general does not affect the outcome of IVF [8,25]. It is noted that despite an increase in the frequency of FII and FV gene mutations, especially in combination, in patients with ovarian hyperstimulation syndrome, is not effective to carry out a total screening before IVF from an economic point of view [7].

As a counter-argument it is suggest that the knowledge benefits about the carriers of mutations in FII and FV genes in IVF patients can not only help with IVF but also to adjust the maintenance of pregnancy to help reduce the risk of fetal loss and reduce the likelihood of gestosis.

An interesting observation was made by Göpel et al. [26]. It was found that during the procedure of IVF in women heterozygous for the Leiden mutation the embryos also obtaining this polymorphism in heterozygous state have overwhelming advantage when implanted. Molecular mechanisms of this selection remain unknown, but the phenomenon can partially explain the fairly wide presentation of Leiden mutation in the European/North American population.

The next polymorphism that has proven its clinical value and been included in the final test panel was −675 5G>4G in plasminogen activator inhibitor gene PAI-I. The corresponding protein is one of the most important factors in plasma hemostasis. Since SNP is located in the promoter region of a gene carrier 4G allele leads to its increased expression which is reflected in the increase in PAI-I levels in the blood, reduction of thrombolytic activity system, increasing the risk of thrombus and is a risk factor for various thromboses.

Although there are some data about influence absence or disputed impact of the 4G allele in the female reproductive system [27], the most research suggests undoubted negative impact of the 4G allele for habitual miscarriage, IVF failure and polycystic ovary syndrome [15,28–30]. Present data confirm this point of view. Apparently the point in this discussion can be delivered by the results of meta-analysis made by Xuejiao et al. [31] that confirm the certain effect of this SNP for the reproductive health of Caucasian women.

The final panel includes two polymorphisms associated with fibrinogen dynamics: L33P T>C of ITGB3 gene and −455 G>A of FGB gene. The ITGB3 gene product is a platelet fibrinogen receptor, beta-3 integrin chain heterodimer complex IIb/IIIa involved in cell adhesion and intercellular signaling. It is a common synonym for glycoprotein-3a (GPIIIa). During activation of this heterodimer platelet interaction with fibrinogen occurs in blood plasma rapidly leading to platelet aggregation at the site of injury of vascular endothelial surface. It was demonstrated repeatedly that allelic variant C of SNP L33P T>C shifts the equilibrium toward increased platelet adhesion [32,33]. The risk of spontaneous thrombosis is increased as a consequence. The significant role of this SNP to women's reproductive health is also reflected in a number of papers [34]. The special importance of ITGB3 for implantation processes is noted by Germeyer et al. [35]. These authors noted a significant decrease in expression of beta-3 subunit of the integrin molecule gene in the endothelium directly to the site of implantation.

The −455 G>A mutation in the FGB gene promoter leads to increased gene expression resulting to increased levels of fibrinogen in the blood and increases the likelihood of spontaneous formation of thrombi [36]. A significant influence of the pathological allele A to habitual miscarriage is presented [6]. The present study also shows the relationship of this SNP genotype with women eproductive disorders.

Controversial debate there is about the role of polymorphisms of platelet receptors in the regulation of pathological processes of thrombus formation. Martinez et al. [37] found no significant effect of pathological alleles on susceptibility to bleeding and thrombosis studying the phenotypic expression SNP of platelet receptors six genes. Potentially possible but still not proven role of these genes in the development of cardiovascular diseases and complications of pregnancy is showed in the study of di Paola et al. [38]. Among the studied SNP were T154M C>T of GP1BA gene and 807 C>T of ITGA2 gene.

The greatest interest for diagnostic tests in this group of polymorphisms has SNP 807 C>T in integrin alpha 2 gene ITGA2 which is one of the reliable markers of cardiovascular disease [39]. Its synonyms are GPIa (glycoprotein Ia), CD49B, VLA-2 (very late activation antigen 2). The complex of integrin subunits alpha-2 and beta-1 is a receptor for laminin, collagen, fibronectin, and E-cadherin. The involvement of this receptor in the adhesion of platelet on collagen wafers and other substrates is shown such as in the reorganization of the extracellular matrix processes. The presence of 807 C>T T allele leads to a changes in the kinetics of platelet adhesion.

Sharp discontinuities of hormonal balance influence on the kinetics of the platelet interaction with the elements of the extracellular matrix [40,41]. Wherein TT genotype of SNP 807 C>T ITGA2 gene significantly increases the thrombophilic risk. The special role of this polymorphism to patients before IVF follows from the Ji et al.'s study [42] which shows the effect of progesterone on the regulation of the interaction of the collagen-binding integrins, including integrin alpha 2 through the mitogen-activated protein kinase signaling pathway. Considering the extreme prevalence of allele T in the Russian population the testing for this SNP in gynecology seems to be important enough.

The composition of the final tests panel due to economic reasons was forced to cut to eight SNP so C>T ITGA2 gene either −455 G>A FGB gene was chosen. However, if possible, both these SNP are useful to test for the data.

SNPs in the folate cycle genes network

The most indisputable hereditary risk factors for vascular complications in female reproduction are polymorphisms of the folic acid cycle genes network [43,44]. The key molecule influencing physiological manifestation of these genes allelic variants is homocysteine. It is an amino acid not involved in protein synthesis. Its predecessor is methionine and for the reverse reaction the B-group vitamins are essential. Free homocysteine is quite toxic compound that violates the integrity of the vascular endothelium. These properties determine the fact that the increased level of free homocysteine is one of the precipitating factors in the development of a number of multifactorial diseases: violation of embryonic development [45], metabolic syndrome (primarily atherosclerosis), lymphomas, all kinds of cardiovascular diseases [46], disorders of pregnancy, autism, Alzheimer's disease [47]. Equilibrium between methionine and homocysteine also defines the correct flow of the fundamental processes such as synthesis of nucleotides and DNA methylation. In connection with the multi-step process and the participation of a significant number of regulators the free homocysteine blood level is dependent of many factors, including age, sex, diet, hormonal balance, the presence of chronic inflammation, exposure to adverse environmental influences (smoking), heredity. It is to hereditary factors SNP in folate cycle genes are related.

A key molecule that determines the balance between the derivatives of folic acid directly and homocysteine/methionine is

an enzyme methylenetetrahydrofolate reductase encoded by the gene MTHFR. This gene has several allelic variants and the presence of pathological alleles causes a decrease in enzyme activity. The presence of the allele T of SNP 667 C > T and allele C of SNP 1298 A > C in various combinations (homozygote/heterozygote) reduces the enzyme activity down to 80% and shifts the equilibrium toward the free homocysteine by increasing its concentration in the blood.

The presence of pathological alleles only in the MTHFR gene does not explain all of the manifold manifestations of violations in folate cycle regulatory genes. To date, it is proved that for assessing the role of heredity in the development of hyperhomocysteinemia at least four SNP in three genes (MTHFR, MTRR, MTR) should be analyzed [44]. It was the SNP the final test panel includes. Two else polymorphisms: 80 A > G in folate transporter gene SLC19A (RFC1) and 1598 G > A in tetrahydrofolate synthase gene MTHFD1 showed no differences in allele frequencies in a problem and the control samples so the final panel does not include its. Since there are some data about the important role of this SNP's rare alleles in the development of hyperhomocysteinemia [48], more study is required.

The apparent advantage of SNP in folic acid cycle genes testing is the possibility of having a simple medical correction of pathologic alleles presence effect: usually prescriptions of folic acid, B group vitamin, and omega-3 fatty acids reduce the level of free homocysteine in blood [49–51]. This is especially actual in key moments of the IVF and the initial stages of pregnancy.

SNPs in the renin-angiotensin system

Renin-angiotensin system is a hormonal regulator of blood pressure and blood volume in the human organism. Its key component is angiotensinogen AGT, the precursor of angiotensin II. It is synthesized in the liver and regulates the vasopressor activity. The AGT gene structure has several SNP pathological alleles in which cause increased angiotensin content in the blood. Blood pressure increases as a result. Polymorphisms T174M C > T and M235T T > C in AGT gene are markers of hypertension, metabolic syndrome, chronic renal failure, thrombosis, and complications of pregnancy (pre-eclampsia) [52–54].

The main cardiovascular effects of angiotensin II caused by angiotensin type I receptor AGTR1 (AT1R). It is the presence of pathological alleles in the AGTR1 gene associated with development of vascular disorders including those not related to blood pressure levels [55,56]. There are also data about the absence of rare allele C of SNP 1166 A > C in AGTR1 gene influence on the violation of pregnancy [57]. The special role of the AGTR1 gene and its polymorphic variants for IVF should be the ensues data by Pringle et al. [58] noted the key role of this gene expression during the maturation of the trophoblast. There are specific pattern of AGTR1expression in the trophoblast cells of the tissues on the border of the mother and the fetus which largely determines the success of early placentation [59]. It is because of these reasons the study of polymorphism 1166 A > C of AGTR1 gene in preparation for IVF may be the key value.

One of the most studied component of the renin-angiotensin system is an angiotensin-converting enzyme ACE. This multifunctional protein plays a key role in processes such as regulation of blood pressure, maintain a balance of electrolytes, platelet activation and aggregation, fibrinolysis. ACE protein functionality and features of its expression, associated with the presence of Alu-sequences in the intron, are devoted to a great number of publications [55,56,60–62]. Virtually all studies agree that the presence of variant D (Del), lack of Alu-sequences in the intron of the ACE gene, is associated with atherosclerotic, cardiovascular disorders and the risk of pregnancy violation [29,61,62]. At the molecular level, Alu insertion reduces the gene expression level that is displayed as s decrease in the level of ACE protein in the blood and more precise regulation of blood pressure without pronounced spikes as a consequence.

The situation with the role of SNP of the renin-angiotensin system genes in the development of clinical complications of pregnancy requires considerable attention due to the huge prevalence of pathological alleles of such SNPs in the Russian population. Since the frequency of the patological allele reaches about 50% in the ACE gene, 30–40% in AGTR1 gene and 15–20% in each of the two investigated polymorphisms of AGT gene about half of the population has a genetic predisposition to multifactorial diseases one of the causes of which is hypertension. Considering such a wide prevalence it is appears to be the greatest effect of renin-angiotensin system genes SNP genotyping can be obtained by the genetic analysis of all four SNP discussed only with clinical indications such as hypertension and metabolic syndrome.

SNP in blood coagulation factors genes which were not included in the final panel

Polymorphism 3872 C > T in the C-reactive protein gene CRP was repeatedly described as a biomarker of a number of multifactorial diseases: atherosclerosis, coronary heart disease, malignant neoplasms, disorders of normal pregnancy and a number of others [63–65]. The study by Kolz et al. [66] showed that the minor T allele SNP 3872 C > T of CRP gene is strongly associated with reduced levels of C-reactive protein in the blood plasma. However significant differences in genotype 3872 C > T gene CRP could not be detected. It is seems to be that processes of implantation and early pregnancy current less dependent on the level of CRP in blood plasma than the initial processes of inflammation. This point of view is consistent with Teran et al. [67].

Coagulation factor VII is a protease and it is involved in the cascade of the blood clot formation. It is shown the clinical value of two polymorphisms of the gene: R353Q 10976 G > A and −323 ins 10 bp (insertion of 10 nucleotides in promoter region). The presence of the minor allele of the gene has a proven protective effect against the development of thrombosis and cardiovascular diseases [68]. In case of SNP 10976 G > A allele A presence enzyme activity is reduced and in case of insertions in the promoter of the gene expression level decreases. The data of this SNP show a clear association of clinical effects with sex: in men it appears significantly stronger [69]. Possible predisposition to bleeding in carriers of these SNP minor variants homozygous requires further study. No differences in the genotype frequencies in females in the usual failure of IVF and the control is not revealed.

Coagulation factor XIII (FXIIIA1) is a common subject of genetic research. Among FXIII protein functions stabilization of cell membranes, involvement in the final step of the coagulation cascade, cross-linking fibrin, fibronectin, and collagen monomers are marked. SNP V34L 103 G > T is closely associated with the risk of thrombosis: it is repeatedly shown a protective effect of T allele against the development of cardiovascular disease [70]. On the influence pathologic alleles of this polymorphism on the risk of early miscarriage reported Dossenbach-Glaninger et al. [29]. There are also the data, the simultaneous and the same authors, describing no effect of genotype on this SNP for venous thrombosis [71]. This study also revealed no role for the development of gynecological pathologies. It is appears to be that if the clinical significance of this SNP is real it is insignificant.

Most of the studied platelet receptor gene SNPs are not included to the final test panel. Pathologic allelic variants of P2RY12 gene influence on intracellular signal transfer and platelet aggregation and are one of the causes for hemorrhagic syndrome [41,72]. Association of H2 version with disorders of pregnancy is noted while noting the different allelic frequency of this SNP between representatives of different population groups [73].

P2RY12 protein belonging to the family of receptors conjugated with G-proteins may cause increased sensitivity to certain drugs. It is noted that this family of receptors is the target of up to 40% of the currently used drugs [74]. Since during the IVF procedure on a woman's body accounts for a large pill burden the P2RY12 receptor and its allelic variants role in the development of thrombosis and bleeding requires further study.

Another platelet surface receptor with different gene allelic variants is a protein GP1BA. It is part of the tetramer which functional tasks are interaction with von Willebrand factor, platelet aggregation, and cell adhesion [39,41,75]. Pathological allele T of SNP T145M 434 C>T in alpha subunit of platelet glycoprotein 1b gene GP1BA is one of the causes of platelet type of von Willebrand disease specifically an increased tendency to bleed. The second manifestation of this gene violation is Bernard-Soulier syndrome [76]. Association of rare T allele of SNP T145M 434 C>T with the varying number of tandem repeats in the gene GP1BA is seems to be interesting enough and requiring further study [77]. In this study, the frequency of rare allele matched in women with habitual failure of IVF and the control group as well as to the literature data.

Endothelial nitric oxide synthase eNOS (NOS3) synthesize nitric oxide, which takes part in vasodilation (vascular muscle relaxation). Nitric oxide also affects angiogenesis and blood clotting. In European populations, the 298D variant of polymorphism E298D 894 G>T is spread. Minor allele T is a marker of cardiovascular complications and it occurs with a frequency of 30–40%. It is also noted the important role of according protein in the processes of placental vessels development and it was shown the influence of pathologic alleles to pregnancy violations [56,78,79]. Although the available data, it is difficult to speak clearly about the role of nitric oxide synthase in the pregnancy disorders development and all the more so IVF failures. Among the reasons are sufficient to indicate a cjmplicated regulation cascade of NO production, as well as the presence of powerful mechanism induced iNOS2 for producing the vast amount (up to 1000 times) of NO in response to provocative effect primarily inflammation in blood cells (macrophages) [80].

A number of studies suggest a possible involvement of some SNP of detoxification system genes in the pathological processes that lead to pregnancy loss [81,82]. Particularly emphasize the role of the protein glutathione transferase pi which is particularly active in the cells of the proximal tubule [83]. On the increase in the value for the assessment of risk disorders for the female reproductive function is GSTP compared with the analogous enzymes GSTM and GSTT says recent observation of Liu et al. [84]. The researchers found that the protein GSTP in addition to participating in the metabolic detoxification as a conjugation reactions enzyme is an active regulator of the estrogen receptor alpha signaling pathway by modifying transcription cofactors, such as RIP140.

The final test panel panel primary included two SNP in glutathione transferase pi gene GSTP1 and one SNP in paroxonase gene PON1. Although the result of the comparison of the frequencies of genotypes showed a significant increase in the incidence of pathological alleles GSTP gene compared with the average in the frequency the detoxification systems genes are not included to the final panel of SNP. The reasons were: (1) extremely high, up to 40%, the incidence of pathological allele G of polymorphism I105V A>G, (2) lack of understanding of the molecular role of the corresponding proteins in the process of maturation of oocytes and implantation which leads to the impossibility of compensating destination therapy.

Paraoxonase enzyme is involved in a wide array of physiological processes such as inflammation, oxidative stress, and lipid metabolism. Inclusion of SNP Q192R A>G in PON1 gene as a candidate for research is due to the availability of data about its significant influence on the development of female infertility [85,86]. This polymorphism also was not included in the final version of the test panel due to lack of information about its role in the development of a number of multifactorial diseases such as female infertility, metabolic syndrome, vascular disorders. It is also not described methods compensatory treatment of conditions caused by decreased activity of paraoxonase especially in IVF [87]. It is seems to be better approach the appointment of testing SNP of detoxification system genes individually to women exposed to the adverse effects of the environment, having contact with toxic substances, kept smoking.

The presence of polymorphism V617F G>T in Janus kinase 2 gene JAK2 among the studied SNP is due to the data on a higher frequency pregnancy interruptions caused by thrombosis in women with this mutation [88,89]. However, somatic type of mutation, a clear correlation with age and the low enough prevalence [90] is hardly allow us to speak about the effectiveness of this SNP testing in preparation for IVF. These data confirm the findings of Grandone et al. [91].

Thus, this experimental way matched panel combines the maximum number of the most valuable genetic information with a relatively small price and is seems to be the best choice for mass testing during preparation for IVF for both doctors and patients.

Declaration of interest

The authors have no relevant financial, personal, political, intellectual, or religious interests. The authors have had full control of all primary data and they agree to allow the journal to review their data if requested.

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