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The Role of Genetic Research in the Reproductive Loss Prevention in Women with Miscarriage

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Abstract The defective combination functionally weakened alleles against the unfavorable (provoking) factors action background of the external and internal environment can lead to pregnancy pathology and impaired embryonic fetus development. Considering the metabolic systems complexity that determines the harmonious interaction between the mother and the fetus, the functional weakening of many genes begins to be realized only during pregnancy.

Keywords Miscarriage, Reproductive loss, Vascular endothelial growth factor (VEGF) genes, Detoxification gene (GSTP1)

1. Introduction

Among the most important tasks of modern obstetrics, the search for possible causes and diagnostic markers of miscarriage is still very relevant. Human reproductive losses are about 50% of the total number of conceptions. The miscarriage frequency remains high, despite the success achieved in the prevention and treatment of reproductive disorders in humans. [1].

One of the leading causes of early miscarriage is considered to be a genetic factor. Genetic analysis of multifactorial pathology, based on the gene polymorphism study, is still a difficult task.

The scientific literature of recent years has accumulated numerous studies and data experience from clinical studies, which make it possible to isolate a folic acid deficiency, an increased homocysteine level and allele's polymorphisms of the folate cycle genes, a separate group of causes that potentiate various obstetric pathologies development. That is why scientific studies on the carriage identification of polymorphic genes variants in women with an unfavorable pregnancy outcome remain interesting [3,10]. Multifactorial diseases are distinguished by the fact that the body is simultaneously influenced by a pathological group and normal genes alleles and the intervention of unfavorable environmental conditions, which leads to the various pathologies development. Therefore, these genes were called "predisposition" genes. However, nowadays, the study and analysis of multifactorial diseases from the perspective of considering the gene polymorphism influence on the emerging pathology remains a difficult task. [2,4].

At the same time, in the literature data of recent years, the emphasis is on the fact that genes for "predisposition", of course, determine the high probability of developing various obstetric pathologies, but they are not always passed on to offspring [6]. It follows from this that studies devoted to the study of various body relationship functions with alleles polymorphism of various genes are of great medical and social importance, and the results obtained by the authors will form the basis for predicting various clinical complications for each individual gene polymorphism [5,7,8,9].

Research in recent years has expanded our understanding of the genetic determinants role and a number of immune factors in miscarriage. [10]. The genes of growth factors in the pregnancy development (namely, in the development of the mother-placenta-fetus system) are represented by a well-coordinated system of cellular reactions regulated by local mediators - cytokines and steroid hormones. [11].

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The most difficult period of pregnancy is the first trimester, which includes the main critical periods: implantation, organogenesis and placentation. The formation stage of the uteroplacental region of the endometrium and ovum placentation is the chorionic villi vascularization and their invasion into the decidual vessels. Angiogenic growth factors play the main role in the cellular components proliferation of the vascular endothelium, endometrium and chorion. 4 polymorphic variants are known in the vascular endothelial growth factor (VEGF) gene: 2578 C/A, 1154 G/A, 634 G/C, 936 C/T. [11,14]. The most significant of these is vascular endothelial growth factor A. (VEGF-A). Growth factor VEGF-A is an extremely specific endothelial cell mitogen that stimulates endothelial proliferation, cell migration and slows down apoptosis of chorionic cells and decidual tissue. Among the proteins of the VEGF family, the growth factor VEGF-A is the most potent pro-angiogenic protein and plays a key role in the regulation of angiogenesis. Growth factor VEGF-A in the vascular endothelium is responsible for two main processes: increased vascular permeability and proliferation of endothelial cells, both events necessary for the successful development of the embryo.

Substitution of amino acids in the nucleotide sequence of the VEGF gene. A can lead to a change in gene expression and, as a consequence, to a decrease or, conversely, to an inadequate increase in VEGF-A level in the mother's blood and in the placenta. In recent studies, the relationship presence between placental vascularization, the angiogenic growth factors expression level and spontaneous abortions frequency has been proven. [20].

In other literature sources, VEGFR2 (KDR / flk-1) is described as more significant, since it mediates the main effects of VEGF, including the angiogenesis stimulation, vascular permeability and cell proliferation. Another group of angiogenic factors present in the endometrium is angiopoietins (angiopoietin-1 and angiopoietin-2). Angiopoietin-1 is a growth factor responsible for the blood vessels development. Angiopoietin-2 is the main growth factor involved in vascular remodeling. Angiopoietin-2 causes a decrease in the endothelial cells interaction with the extracellular matrix and with each other, which stimulates VEGF activity. The joint expression of antiopoietin-2 and VEGF leads to an increase in the processes of angiogenesis [8]. Changes in the angiogenesis processes in the endometrium can lead to the cyclic transformation disruption of the endometrium and, consequently, impaired implantation. Further study of the angiogenesis processes occurring in the endometrium during the implantation period is one of the promising directions for understanding the causes of non-pregnancy and the possibility of their correction [9].

This means that a decrease or imbalance in growth factors in women with miscarriage may be genetically determined. The polymorphism study and gene expression features of chorionic and placental growth factors is important for the tests development for presymptomatic diagnostics and miscarriage prediction, and in the future will allow a new pathogenetic therapy development for this pathology. The most effective method of preventing pregnancy loss is pre-conception and pre-conception preparation. Particular attention should be paid to early, pre-symptomatic detection of women at high risk of miscarriage. [22,25].

The research purpose: improving methods of preventing reproductive losses based on the study of angiogenesis factor gene polymorphism in mothers with recurrent miscarriage.

2. Material and Research Methods

To achieve this goal, 155 women with the usual fetal loss syndrome were assessed, which, depending on the genetic polymorphism of the miscarriage genes, were divided into two groups: group I - 50 non-pregnant women with a history of miscarriage, group II - 70 women with a miscarriage in the first trimester. The control group consisted of 25 women with an unburdened obstetric and gynecological history.

DNA was isolated from all women and polymorphism of the angiogenesis gene (VGFA 634) was examined by PCR diagnostics. Statistical research methods with the calculation of mean values, standard error, Student's t-test, correlations, sensitivity, specificity and predictive value of various tests were carried out.

3. Results and Its Discussion

Miscarriage is a multifactorial disease resulting from the action of functionally weakened variants (alleles) of many genes against the background of unfavorable external and internal factors. [17,23]. Currently, various types of spontaneous abortion are considered as multifactorial diseases, the development of which can be triggered by a combination of several factors. The individual contribution of each factor may be insignificant, and only their sum leads to the disease development. [16,23].

According to the survey, the average age of women was 32.6 + 0.33 years, ranging from 22 to 44 years. Women of the following age groups predominated: 30-34 years (41%), 25-29 years (23,5%). Women over 40 years old accounted for 5.6% of all patients with recurrent miscarriage.

In our studies, one in four to five women with spontaneous miscarriages at work faced occupational health problems in the present or in the past. Out of the somatic diseases, the urinary system diseases (30%) predominated, mainly of an inflammatory nature (cystitis, pyelonephritis), were diagnosed in 64.3%, and of the gastrointestinal tract (24%), autoimmune diseases (autoimmune thyroiditis, systemic lupus erythematosus, rheumatoid arthritis and multiple sclerosis) were noted in 13.3%. When analyzing the gynecological morbidity of inflammatory diseases of the pelvic organs and an urogenital infection history in patients was 30.9%, uterine fibroids - 15.7%, endometrial pathology in 15.2% (hyperplasia 7.8% and endometrial polyps 7.4%,

respectively), intrauterine synechia - in 9.1%, pathology of the cervix against the background of inflammatory changes - in 14.8% of women with habitual early miscarriages. Congenital anomalies of the uterus (saddle, two-horned uterus, intrauterine septum, doubling of the uterus) were verified in 10% of women. Among the hormonal disorders leading to miscarriage, a large place is occupied by hyperprolactinemia and hyperandrogenemia, their frequency in patients with PNL fluctuates 12.1-32%.

In the analysis of the frequency distribution of the Ile and Val alleles of the G634C polymorphism in the subgroups of non-pregnant and pregnant women, the G allele slightly prevailed among non-pregnant patients: 66% versus 58%, and allele C among pregnant patients 34% versus 42% (χ^2=1.2; p=0.3; RR=0.8; 95%CI: 0.532; 1.185; OR=0.7; 95%CI: 0.356; 1.336). The frequency of the wild homozygous genotype G/G prevailed among non-pregnant patients in subgroup 1.1, relative to pregnant patients in group 1.2 (40.6% versus 26.9%, relatively; χ^2=1,5; p=0.2; RR=1.5; 95%CI:0.75-3.036; OR=1.9; 95%CI: 0.683-5,048). The frequency of the heterozygous G / C genotype prevailed among pregnant patients of subgroup 1.2 compared with subgroup 1.1 of non-pregnant patients: 51.6% versus 61.5%, relatively (χ^2=0.7; p>0.4; RR=0,8; 95%CI: 0,57; 1,232; OR=0,7; 95%CI: 0,263; 1,686). The frequency of the unfavorable C/C genotype in the studied subgroups prevailed in the subgroup of pregnant women, and amounted to: 7.8% versus 11.5, relatively (χ^2=0,3; p>0,6; RR=0,7; 95%CI: 0,174; 2,63; OR=0,6; 95%CI: 0,143; 2,942).

An increasing number of studies in the angiogenesis as such and angiogenic growth factors, in particular, confirm that physiological angiogenesis is one of the key processes in human reproduction. At present, it can be considered proven that dysfunction of the angiogenesis process can be considered as one of the key pathophysiological factors that determine the development of diseases of the human reproductive system. Numerous studies have examined the genetic association of vascular endothelial growth factor (VEGF) polymorphisms with recurrent pregnancy loss. In general, our data confirmed the information of the modern literature on the participation of the G634C polymorphism in the VEGFA gene in the pathogenesis of repeated miscarriages [8,11,13,23].

Thus, a significant relationship was revealed between the risk of miscarriage and the carriage of predisposing and protective variants of the rs2010963 polymorphism of the VEGF gene. The allelic 634G variant of this gene is associated with an increased, and the 634C variant with a reduced risk of miscarriage.

Today, it is known that a single integrating system of growth factors exists in the human body, which plays a major role in the processes of tissue growth and differentiation, intercellular cooperation, hematopoiesis, angiogenesis, etc. [2,3,4]. Growth factors in the development of pregnancy (namely, in the development of the mother-placenta-fetus system) are represented by a well-coordinated system of cellular reactions regulated by local mediators - cytokines and steroid hormones.

Placentation is initiated by the interaction of the cytotrophoblast with the decidual endometrial tissue. From the 3-4th week of pregnancy, the trophoblast gradually invades the walls of capillaries, arterioles and small spiral arteries. By 8–10 weeks, trophoblast invasion spreads to the endometrial segments of the spiral arteries. The nature of the paracrine relationship between the trophoblast and the endometrium is determined by the local activity of hormones and growth factors [16]. The decidual changes severity depends on the level of estrogens and insulin-like growth factors in the endometrium. In the proliferative activity control of trophoblast cells, an important role is played by both growth factors and progesterone.

Deviations in a full-fledged vascular system formation of the chorion are attributed to the main factors in the pathogenesis of such frequent obstetric pathology as late toxicosis, placental dysfunction and miscarriage [17,21]. Deviations in a full-fledged vascular system formation of the chorion are attributed to the main factors in the pathogenesis of such frequent obstetric pathology as late toxicosis, placental dysfunction and miscarriage [17,21]. [6,11,20].

The role of growth factor gene polymorphism in miscarriage is just beginning to be studied.

4 polymorphic variants are known in the vascular endothelial growth factor (VEGF) gene: 2578 C/A, 1154 G/A, 634 G/C, 936 C/T. Polymorphism in 1154 G / A of the VEGF gene is represented by 2 alleles: G — normal and A — mutant. In homozygotes for allele A, the VEGF level in the blood is significantly lower than in individuals with the G/G genotype. This indicates the influence of this polymorphism on the expression of the VEGF gene [11].

It is known that during miscarriage, the level of growth factors in the mother's blood is reduced. Thus, in women with a spontaneous miscarriage that has begun and / or a missed pregnancy in the first trimester of pregnancy, the concentration of VEGF in the blood serum is reduced by 2 times, and the level of insulin-like growth factor I is reduced by more than 4 times compared to normal pregnancy. [11,12].

The frequency of the 1154A allele of the VEGF gene in women with three or more spontaneous miscarriages in history was significantly higher than in the control group [11]. An association of the 936 C/T polymorphism of the VEGF gene with the risk of miscarriage has also been established. Thus, in patients with habitual fetal loss, the C/T and T/T genotypes were diagnosed 1.5 times more often than in the norm.

Thus, a decrease or imbalance in growth factors in women with miscarriage may be genetically determined. The study of polymorphism and features of gene expression of chorionic and placenta growth factors is important for the development of tests for presymptomatic diagnostics and prediction of miscarriage, and in the future will allow the development of a new pathogenetic therapy for this pathology.

The process of detoxification of xenobiotics is carried out

by a complex system of enzymes; one of the main enzymes of phase II of detoxification is the family of glutathione-B-transferases (GST) [15]. It is known that GSTs are present in a wide variety of tissues, and begin to be expressed as early as the embryonic period of development [335,339]. Polymorphism of genes that control their synthesis can lead to an increase or decrease in the activity of glutathione-B-transferases, and thus, cause an imbalance of enzymes in phases I and II [2,4,15]. It is logical to assume that the result of such an imbalance may be the accumulation of various toxins in the body of the mother, father and fetus, leading to the threat of early termination of pregnancy.

The frequency of the "functionally weakened" genotype GSTMl 0\0 was significantly higher in the group of women with 3 or more miscarriages and in women with primary miscarriage. At the same time, in patients with miscarriage, there were no significant differences in the frequencies of the GSTT1 and GSTP1 genotypes. The combined genotype GSTMl 0\0 GSTT1 0 \ 0 was diagnosed reliably more often in patients with both one and two and 3 or more miscarriages compared with the control. Also, this genotype GSTMl 0\0 GSTT1 0\0 was determined significantly more often, both in patients with primary and secondary miscarriage. [2,4,15].

When studying the polymorphism of 3 detoxification genes (GSTMl, GSTT1, GSTP1} in men from couples with different numbers of miscarriages, we did not obtain statistically significant results. However, in men from couples with primary NB, a significant increase in the frequency of genotype GSTMl + GSTT1 0\0 GSTP1 A\S.

In a comparative analysis of the frequencies of genotypes and alleles of these 3 genes in women with different numbers of miscarriages, interesting data were obtained. Thus, in pairs with 3 or more miscarriages, the GSTP1 A\B genotype was determined reliably more often. Regardless of the number of miscarriages in the anamnesis, the “functionally weakened” GSTMl 0\0 GSTT1 0\0 genotype was determined reliably more often. In couples with one miscarriage, one of the spouses was significantly more often a carrier of the GST1 0\0 genotype. In the group with 3 or more miscarriages, both spouses were significantly more likely to be carriers of the combined genotype GSTMl 0\0 GSTT1 0\0 [2,4,15].

It is known that the GSTP1 gene controls the synthesis of an enzyme, which is expressed mainly in the reproductive tract and placenta [2,4,15]. In this regard, the authors suggested that in the presence of a functionally weakened genotype, inactivation of xenobiotics in the placenta occurs especially slowly. In such conditions, the adverse effect of toxic metabolites on the body can manifest itself quite strongly and significantly increase the risk of placental insufficiency and, as a result, intrauterine growth retardation of the fetus. According to the study, in patients with the A\C genotype of the GSTP1 gene, the relative risk of developing placental insufficiency is increased by 4 times.

During pregnancy, the antioxidant system of the body experiences the greatest stress associated with protecting the developing and growing embryo. Therefore, even a slight decrease in the activity of enzymes of the antioxidant system, associated with the variability of the genetic basis, can lead to serious violations in the development of pregnancy. Living conditions in a modern metropolis aggravate the effect of the oxidative system on the woman's body through psychoemotional overstrain, toxic effects of chemicals, and disturbances in biological rhythms. Modern personalized medicine sets itself the task of identifying unfavorable "predisposition genes" that can reduce the activity of the body's defense systems. Therefore, analysis of allelic polymorphism and enzyme activity of xenobiotic detoxification and antioxidant defense systems can make an invaluable contribution to identifying risk groups for miscarriage to reduce reproductive losses in the 1st trimester of pregnancy [2,4,6,11,15].

The study of genes of phase II of detoxification will identify groups of patients with "fast" and "slow" metabolism of xenobiotics and determine the tactics of therapeutic and preventive measures in solving the miscarriage issue [2,4,6,11,15].

Discovered over the past 10–15 years, the most important genetic factors of many multifactorial conditions, such as thrombophilia, disorders of the detoxification system, defects in folate metabolism, hormonal deficiency, immunological failure, etc., can act as the leading causes of severe obstetric pathology (miscarriage, dysfunction of the placenta, intrauterine growth retardation, late toxicosis).

At the phenotypic level, the genetic factors implementation often leads to an unfavorable hypercoagulable background formation, an increased concentration of toxic products, endothelial cells pathology, hormonal insufficiency, and immunological activity. However, taking into account the compensatory capabilities of the organism, the changes observed at the gene level require direct confirmation at the biochemical level. Changes at the gene level (polymorphisms) only create the necessary prerequisites for the development of multifactorial pathology. The human body has a complex hemostasis system with adaptive properties. With a defective combination functionally weakened alleles against the unfavorable (provoking) environmental factors action background, such polymorphisms can play an important role in the pathology of pregnancy and impaired embryonic development. [2,4,6,11,15].

The possibility of early pre-symptomatic diagnosis of any obstetric pathology allows for preventive treatment and prevents the disease from manifesting itself. This is especially important for patients who have a genetic predisposition to its development.

The obtained and studied data make it possible to scientifically substantiate the predictive significance of genotype polymorphism in miscarriage. However, given that these predictors are predisposition genes that potentiate the development of various pathologies, it is important at the pregnancy planning stage to level their effect by replenishing the folic acid and B vitamins deficiency. [18,19].

Therefore, we have proposed an algorithm for pre-gravid preparation in women with a history of miscarriage, including the appointment of progesterone derivatives (Duphaston) for 3-6 months, providing gestagenic support for the endometrium and increasing the immunity of women, as well as folic acid at a dose of 400-800 mcg per day.

Folic acid is a critical nutrient during pregnancy and lactation. Folate deficiency during pregnancy is often associated with adverse outcomes such as fetal malformations (cardiovascular, nervous systems, limbs, visual organs), miscarriage, antenatal fetal death, developmental delay, preeclampsia, premature placental abruption, and premature birth.

Folic acid plays a protective role in pregnancy in relation to the action of teratogenic and damaging factors on the fetus and is involved in the normal maturation and functioning of the placenta. Folate requirements increase during pregnancy as they are needed for the growth and development of the fetus. Folate deficiency is associated with the development of disorders both in the mother (anemia, peripheral neuropathy) and in the fetus (congenital malformations).

Taking folic acid 400–800 mcg per day before and after conception protects against the risk of developing structural abnormalities in the fetus, including neural tube defects and congenital heart defects, and may also protect against the risk of preterm birth [18,19,24]. We included vasoactive drugs in the complex of rehabilitation measures to correct the hemostasis parameters. Especially in pre-gestational preparation, it is necessary to carry out therapy with antithrombotic drugs that improve blood flow in the vessels of the uterus.

In case of detecting violations of blood flow in the uterine vessel system (according to ultrasound and Doppler measurements), regardless of the state of the endometrium, 25 mg of courantil was used for 2-4 cycles 3 times a day from the 7th to the 28th day of the cycle. In the case of severe hypercoagulation with the appearance of markers of intravascular coagulation, we used low molecular weight heparins.

4. Conclusions

Thus, taking into account the important role of folic acid and B vitamins for the favorable course of pregnancy and the physiological development of the fetus, it is necessary at family planning stages, pregravid preparation and in the first trimester of pregnancy to conduct conversations/consultations with women about the need for timely and regular intake of these drugs in order to leveling of genetic predictors, especially for women with a miscarriage history and folate cycle genes polymorphism.

Identification of the polymorphic and mutational carriage variants of genes is of great and undeniable significance, and prevention and timely correction of pathological manifestations of mutant genes ensures the normal course of pregnancy. In addition, when assessing risks according to foreign authors, not only analysis of the influence of individual alleles of polymorphic genes is of great importance, but it is also necessary to approach in detail the study of their combinations, since it is the combination that in turn forms the genetic predisposition of the woman's body to miscarriage.

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