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CURRENT UNDERSTANDING OF THE PATHOGENESIS OF HABITUAL PREGNANCY FAILURE

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Abstract: Adequate screening and identification of the causes of pregnancy failure in each case allows the development of optimal methods for prevention and rational preparation of couples with a history of reproductive losses for subsequent pregnancies and to achieve successful completion of pregnancy.

Keywords: pregnancy failure, gene polymorphism, gene alleles, risk factors.

INTRODUCTION

Currently, the problem of pregnancy failure remains one of the leading problems in modern obstetrics. Despite the achievements of modern medicine, the problem of miscarriage of pregnancy (MP) has not lost its urgency because it entails not only violations of reproductive function of women but also has a negative impact on the birth rate, causing a significant increase in perinatal mortality and neonatal morbidity [1,9,23,28].

The relevance of this problem is associated with the prevalence of this pathology in the structure of reproductive losses, accounting for 15-20% of all clinically detected pregnancies, about half of which are premature births. The incidence of MP reaches 50-70% in the first trimester, 18-20% in the second trimester, and 7-30% in the third trimester. The maximum number of spontaneous abortions (81.1%) is seen in the first trimester, with 38% of them in the first 7-8 weeks [73,182,185]. Early abortion (4-5 weeks), which represents 8% of all pregnancies, often goes unrecognized [23,28].

MP in the third trimester is the cause of over 50% of stillbirths, 70- 80% of early neonatal mortality, 60-70% of infant mortality. Premature infants die 30-35 times more often than full-term babies, and perinatal mortality in MP is 30-40 times higher than in term birth [23,28]. In 12.6% of pregnant women with a history of habitual miscarriage, there is a delay in fetal development [23].

Therefore, the search for informative markers-predictors of this pregnancy complication is of certain scientific and practical interest. Prediction and preclinical diagnosis of fetal abnormalities are of particular importance (23).

The term "recurrent pregnancy loss" rather than miscarriage is now accepted in the world literature. This is due to the fact that in the first trimester, 75% of pregnancies first result in fetal/embryonic death, and only then there is the possibility of a threatened abortion or miscarriage. Due to the possibilities of ultrasound, the diagnosis of an incomplete pregnancy or an embryo is often made before the onset of clinical symptoms of miscarriage.

Currently, the following leading causes of habitual pregnancy loss are distinguished:

1) genetic;
2) endocrine;
3) immunological (autoimmune, alloimmune);
4) infectious;
5) thrombophilic;

6) uterine pathology (malformations, genital infantilism, uterine hypoplasia, isthmic- cervi

Rapid development of human genetics in the late XX and early XXI century led to the understanding that the basis of all diseases, both hereditary and multifactorial, belongs to genetic factors [16,20,25]. This also applies to the pathology of the reproductive system.

Failure to conceive is a multifactorial disease: the result of functionally weakened variants (alleles) of many genes against the background of unfavorable external and internal factors.

One of the most pressing problems of medical genetics is the control of genetic and adverse environmental factors affecting the human genome, i.e., leading to an increase in genetic load in populations [16]. The concept "genetic load" is interpreted widely enough: in the prenatal period it is sterility (5-10% of sterile marriages are genetically determined), spontaneous abortions (20% of all pregnancies), stillbirths, birth of immature fetuses, congenital malformations. In the postnatal period - monogenic and multifactorial hereditary diseases [3,12].

Multifactorial diseases are determined by many genes, or rather by large groups of functionally related genes (gene networks). More than 1,500 genes whose mutations are widespread in populations and are allelic variants of genetic polymorphism have now been identified. When applied to a large population or mankind as a whole, genetic polymorphism is viewed as a variety of genotypes caused by qualitative and quantitative variations in a DNA molecule, which in turn cause changes in protein structure and determine the biochemical individuality of each individual [2,3,12,16,20,25]. the phenotypic expression of genetic polymorphism is far from always neutral. It can lead to the synthesis of proteins with altered physicochemical properties, distorted functional activity and thus predispose to various diseases [2,3,12,16,20,25].

Such functionally "weakened" alleles were called "predisposition genes" [16,25]. testing alleles of "predisposition" genes is important for the prevention, treatment and prognosis of the course of various diseases of different etiologies - multifactorial, gene and infection [2,3,12,16,20,25]. It should be noted that hereditary predisposition to any obstetric pathology (MP, gestosis, placental insufficiency) does not imply transmission of this pathology to the offspring as such, but assumes inheritance of the corresponding alleles of "predisposition" genes that determine the probability of developing this disease [12]. The relationship between genetic variants and body functions draws attention of many researchers, because it allows more precise determination of the clinical significance of each specific polymorphism.

Detoxification genes. Studies in recent years have shown that the susceptibility of the body to harmful environmental influences depends on the activity of enzymes of the xenobiotic detoxification system. The process of xenobiotics detoxification is carried out by a complex metabolic system in which over 200 enzymes are involved [2,3,12,16,20,25]. The entire detoxification process occurs in three stages (phases). In phase I, enzymes (cytochromes P450, microsomal epoxyhydrolases) bind xenobiotics to form genotoxic intermediate electrophilic metabolites; in phase II, with the help of enzymes (glutathione-S-transferases, N-acetyltransferases, UDF-glucor-onsulfotransferases) the transformation of intermediate electrophilic metabolites into water-soluble nontoxic derivatives occurs. The joint functioning of phases I and II of detoxification is particularly effective. Phase III involves the removal of detoxification products from the body via the lungs, kidneys, and intestines [2,3,12,16,20,25].

The group of phase II detoxification genes is represented by the glutathione-8-transferase (GST) superfamily, which catalyzes the interaction of glutamate with electrophilic atoms N, C, S, O and is responsible for the conjugation of sulfhydryl groups with xenobiotic molecules. Glutathione-mediated detoxification plays a key role in deactivation of lipid peroxidation products (LPP) and DNA peroxides, they restore organic hydroperoxides into alcohols and isomerize some steroids and prostaglandins. Intensification of LPP associated with polymorphism of detoxification system is known to have toxic effect on cell biomembranes. It is also shown that disbalance in lipid peroxidation - antioxidant system (AOS) may be caused by decreased concentration in blood of steroid hormones that possess antioxidant properties, which is also essential in pathogenesis of MP [2,3,12,16,20,25].Class mu glutathione-S-transferases are divided into 5 groups: GSTM1, GSTM2, GSTM3, GSTM4, GSTM5.

All these forms are synthesized from a single gene GSTM1, mapped on the long arm of chromosome 1. The GSTP1 gene is located on chromosome 11; its protein product is one of the most important GST isoforms in the reproductive tract and placenta. The GSTT1 gene is mapped on chromosome 22 [2,3,12,16,20,25]. it is known that GST are present in a variety of tissues and start to be synthesized in the embryonic period of development. Polymorphism of the genes controlling their

synthesis may lead to an increase or decrease in the activity of the corresponding enzymes, and thus be the cause of an imbalance between phase I and phase II enzymes. It is logical to assume that the consequence of this imbalance may be the accumulation of various toxins in the mother, father, and fetus, leading to the threat of early pregnancy termination.The results of studies of gene polymorphism of the detoxification system in HPF are mixed. In 1996, Hirvonen A. et al. [20] showed an association of functionally impaired alleles of the GSTM1 gene with habitual early fetal loss.

However, the Swedish authors [25] did not find any association of functionally impaired GSTP1 gene alleles with the risk of HPF. Japanese researchers confirmed the role of "functionally impaired" GSTM1 0/0 genotype in a woman with HPF [16]. In Russia, the study of gene polymorphism of detoxification system in HPF was performed in the Northwestern and Central regions, and the study was conducted not only on women but on married couples with impaired reproduction in general [2,3,12,16,20,25]. We studied the polymorphism of three genes GSTM1, GSTT1 and GSTP1 in 264 couples with a history of abnormal reproduction in the Northwestern region from 1999 till 2007. There was found a reliable association of HPF with the presence of functionally impaired alleles of 3 phase II genes GSTM1, GSTT1 and GSTP1 [2,3,12,16,20,25]. Moscow scientists found no statistically significant differences in the frequencies of polymorphic alleles in genes of the detoxification system between individuals with normal and impaired reproduction.

Genes of folic acid and vitamin B12 metabolism. In the past decade, a group of genes involved in folic acid and vitamin B12 metabolism has been well studied. High concentrations of the active form of folic acid are required to convert excess homocysteine to methionine. The enzyme cofactors of methionine metabolic pathways are vitamins, the most important of which are folic acid, pyridoxine (vitamin B6), cyanocobalamin (vitamin B12) and riboflavin (vitamin B1). The folate cycle is a complex cascade process involving many different enzymes. The main 4 enzymes involved in the conversion of folic acid at different stages of the cycle are MTHFR, MTRR, MTR and TC. Reduced activity of these enzymes is known to be one of the important causes of homocysteine accumulation in the body.

There are several possible causes of increased homocysteine activity in women and the fetus:the damaging effect of homocysteine on vascular endothelium and stimulation of thrombosis leads to a number of pregnancy complications, including placental abnormalities and disorders of feto-placental circulation, which may result in infertility and MP; increased homocysteine levels in later pregnancy may cause placental insufficiency, and as a result, delayed fetal development and chronic hypoxia. There is a positive correlation between homocysteine levels in the blood of pregnant women and the severity of gestosis.

One of the important factors contributing to the increase in homocysteine levels in blood may be a hereditary predisposition.

MATERIALS AND METHODS

To date, the polymorphism of MTHFR, MTRR, MTR, TC genes has been studied. The products of these genes are enzymes involved in the same metabolic cascade. A number of researchers have noted a significant increase in the risk of obstetric pathology associated with elevated blood homocysteine levels in the presence of polymorphic alleles in several folate cycle genes. Reliable association with reproductive pathology, particularly with MP, was shown for polymorphisms of the MTHFR, MTRR, MTR, and TC genes. The polymorphism of MTHFR C/T gene is the most studied one. The C-677-T allele is the result of a point mutation in which alanine is replaced by valine.

The normal allele is C and the mutant allele is T. The thermolabile 677T variant is associated with impaired folate metabolism, resulting in increased homocysteine levels and thrombophilia. Carriers of the T allele have folic acid deficiency during pregnancy.

Despite the large number of studies that studied the C/T polymorphism of the MTHFR gene in patients with a history of MP, so far there is no consensus about the presence of this association.

According to some data, not only the maternal genotype but also the fetal genotype is more important in MP. Abortion studies have shown a significant increase in the risk of NF (14-fold) in the presence of homo- or heterozygous alleles of the MTHFR 677T and/or 1298C gene in the embryo. Given the important role of folic acid in the metabolism of nucleic acids and, consequently, in the processes of proliferation and differentiation, the violation of folate cycle enzymes is extremely dangerous for rapidly dividing cells of the embryo.

Elevated homocysteine levels may be accompanied by the development of secondary autoimmune reactions and is currently considered to be one of the possible causes of antiphospholipid syndrome [7]. Thus, according to Brazilian researchers, the frequency of 677T allele (40.3%) was significantly higher in women with a history of HPF and antiphospholipid syndrome compared to controls. This allele is considered to be a predisposing factor for thrombosis in HPF.

Another quite frequently studied polymorphism is MTHFR A1298C. The association of this allelic variant with HPF has been shown. Increased frequency of AHC and CHC genotypes of MTHFR gene was registered in women with a history of early second miscarriages. It is noteworthy that no two polymorphic variants of MTHFR gene on the same chromosome were found simultaneously in the studied groups. This testifies to independent occurrence of polymorphisms: C677T and A1298C. It is not excluded that simultaneous presence of two substitutions in MTHFR gene in one chromosome is legal. Exactly, such abnormal genotypes were observed by Isolato R.A. et al, 2000 in their work on abortive fetal material [6].

The polymorphism of MTHFR C677T and MTRR A66G genes has been most fully studied. A pronounced association of these polymorphisms with HPF as well as Down syndrome and spina bifida has been shown [6,7].

An association of two MTRR (A66G) and MTR (A2756G) polymorphisms with HPF has been found. Thus, a recent study (Engel S.M. et al., 2006) showed an increased frequency of 66A allele of MTRR gene and 2756G allele of MTR gene in women with a history of preterm labor (after 22 weeks of pregnancy) [2,3,12,16,20,25].

Clotting factor genes. The development of thrombotic complications is a serious problem of modern obstetrics. The occurrence of microthrombosis in pregnancy is a frequent cause of a variety of obstetric pathology (gestosis, placental insufficiency, premature detachment of normally located placenta, habitual fetal loss, etc.) [6,8,16,21].

It is known that uncomplicated pregnancy leads to physiological adaptation in the hemostatic system, characterized by a stepwise increase in the general coagulation potential of blood due to an increase in activity and quantitative content of most blood clotting factors by 1.5-2.5 times and a decrease in anticoagulant potential. Thus, pregnancy increases the risk of thrombophiliac condition development due to both genetic and exogenous factors.

The most common cause of thrombophilia is resistance to activated protein C, namely mutations of blood clotting factor V Three main mutations of the gene located on the short arm of the chromosome are known: Leiden mutation (G1691A) (FV), Cambridge mutation and Gon-Gon mutation. Carriers of G1691A Leiden mutation in the population are 4-6% of the population. Heterozygous and homozygous forms of FV mutations are considered risk factors for obstetric pathology. Thus, mutations of this gene account for up to 15% in the structure of fetal loss syndrome causes and almost 30% in the development of preeclampsia. The presence of FV gene mutations in women increases the risk of thrombosis throughout pregnancy by 8-fold and premature detachment of the normally located placenta by 10-fold [6,8,16,21].

Some researchers find an increased frequency of the Leiden mutation in women with HPF [6,8,16,21], others in the FII gene [289,379,394], while others do not confirm the association of these polymorphisms with HPF [6,8,16,21]. This may be due to differences in sample sizes, in patient selection when forming groups, and in population characteristics of populations in different countries. The high frequency of several mutations in blood clotting genes in patients with NSB draws attention. Several studies have shown an increased frequency of FV and G20210A mutations in the FII gene in women with recurrent fetal loss at late terms (after 20 weeks of gestation) [6,8,16,21]. Other authors note the association of these mutations with repeated spontaneous miscarriages, both early and late [6]. Contradictory data have also been obtained. For example, some researchers have found no association of mutations in the FV and FII genes with the development of HPF [8]; others have shown a significant association of habitual fetal loss in the first trimester of pregnancy with the presence of the G\A genotype of the FII gene ($p<0.027$) [16]. According to other data, almost 30% of women with a history of three recurrent miscarriages have FV, and the frequency of G20210A mutation of FV gene did not differ from control [21]. One study, however, found no significant association between HPF in women with antiphospholipid syndrome and mutations in the FV and FII genes [6,8,16,21].

Endothelial dysfunction genes. It is known that endothelial dysfunction is the main link in the pathogenesis of many diseases including obstetric pathology: gestosis, placental insufficiency, MP.

Endothelium synthesizes substances involved in blood coagulation and fibrinolysis, regulation of vascular tone and permeability, angiogenesis, etc. Under damage endothelial cells start to produce procoagulants, vasoconstrictors and growth factors [6,8,16,21].

Recent studies have shown that among the etiopathogenetic risk factors of MP the leading place belongs to endothelial dysfunction, both in the maternal organism, and in the feto-placental complex and in the umbilical arteries [6]. Angiotensin-converting enzyme (ACE) (the key enzyme of renin-angiotensin system) is known to be one of the important links in maintaining the balance between vasoconstriction and vasodilation factors and, therefore, in the regulation of vascular tone. This enzyme controls the conversion of angiotensin I into angio-tensin II, which in its turn is one of vasoconstrictors [8,16]. Changes in the levels of vascular metabolites play an important role in the functioning of the feto-placental complex and can lead to disruption of blood circulation regulation in the placenta.

The association of AE gene polymorphism with this obstetric pathology has been established in a few works devoted to the study of MP genetics [6,16,21]. Insertion/deletion (I/D) of the 287-bp Alu repeat in the 15th intron of the ACE gene is of great importance in the regulation of vascular tone. According to a number of researchers, the I/D polymorphism is associated with changes in ACE gene expression level [8]. The presence of the D allele correlates with a significant increase in the amount of ACE in blood plasma. ACE I allele is functionally less active than /E allele. The association of ACE gene D allele with cardiovascular diseases, in particular, with hypertension [8] and with some forms of gestosis has been proved [8]. Significant differences in the frequency of D\D genotype of ACE gene and 4G\4G genotype of PAI-1 gene were revealed between patients with HPF and controls [8]. A positive correlation between these genotypes and increased PAI-1 blood concentrations and hypofibrinolysis in women with habitual fetal loss was established.

The angiotensinogen gene (AGT) is a component of the renin-angiotensin system, a precursor of angiotensin-2. Renin cleaves decapeptide from angiotensinogen, from which angiotensin-2 is subsequently formed. Angiotensinogen, angiotensin-2 and angiotensin-2 receptors are known to be expressed throughout pregnancy in chorionic and fetal tissues [16]. Two known AGT gene polymorphisms, T174M and M235T, are risk factors for hypertension, myocardial infarction, and preeclampsia. The association of M235T polymorphism with increased angiotensinogen blood levels has been shown [21]. A significant increase in the frequency of the M235T polymorphism T/T genotype of the AGTu gene has recently been found in women with intrauterine fetal retardation developed against the background of preeclampsia ($p<0.01$) and without gestosis ($p<0.001$) [8]. A significant increase in the frequency of this genotype was also found in newborns with intrauterine developmental delay ($p<0.001$).

Gene of tissue plasminogen activator inhibitor type-1 (PAI-G) is a central component of fibrinolytic system. It inhibits urokinase, protein-C and tissue plasminogen activator. The 4G\5G polymorphism of PAI-1 gene is associated with PAI-1 activity in blood and the 4G allele is associated with higher levels of PAI-1. This polymorphism is a risk factor for thrombosis, myocardial infarction, gestosis, fetal hypotrophy, stillbirth etc. [6,8,16,21].

The formation of vasoactive substances plays an important role in the development of these processes. Among them, nitric oxide (NO) that possesses marked vasodilatory properties has a special place [21]. According to current understanding, nitric oxide plays the role of a universal regulator of many physiological processes including maintenance of cardiovascular homeostasis, immune status, cytotoxic activity of macrophages, etc.

Hormone metabolism genes. It is known that with insufficient ovarian function, pregnancy is usually terminated in the first trimester [16,21]. Examination of women with LB shows a lack of the luteal phase of the cycle in 44% of cases [6,8,16,21]. As a rule, these violations have a latent character. In the blood of such women, progesterone and estrogen levels are not always reduced, but insufficiency of hormones is almost always accompanied by impaired folliculogenesis. The consequence of an incomplete follicle is an incomplete corpus luteum and insufficient progesterone production. The latter leads to a disturbance in the secretory transformation of the endometrium and its receptivity to sex hormones: progesterone and estrogen. Desynchronization of endometrial development disrupts the implantation process of a fertilized egg, resulting in a spontaneous termination of pregnancy. The pathogenetic mechanisms of this pathology (including MP) are very heterogeneous [8]. The genetic aspects of this problem have been insufficiently studied.

Several papers have been published analyzing the association of an allelic polymorphism in the progesterone receptor gene (PGR) with MP. Progesterone receptor mediates physiological effects of the hormone. It exists in two isoforms, PR-A and PR-B. PR-A prevents cell proliferation induced by estrogen or progesterone while PR-B potentiates it. Several major mutations of the progesterone receptor gene located on the long arm of chromosome 11 are known: A 331G/AV polymorphism in the promoter part of the gene and a 1031G/C polymorphism in exon 1, 1978 G/T in exon 3, 2310 C\T in exon 5, an insertion in intron G called PROGINS, etc.

The 331G/PGR gene polymorphism is known to increase the expression of the PR-B isoform and is associated with endometrial and breast cancer. Recent studies demonstrated association of 331G/Apolymorphism with blood prolactin levels in 270 women of reproductive and premenopausal periods [21].

A significant increase in the frequency of 3 mutant alleles 1031C, 1978T, 2310T of PGR gene was shown in the group of patients with PMP ($p<0.008$) [242]. However, another study did not find any association between PROGINS insertion polymorphism of the PGR gene and MP [16].

Significant differences in the frequency of the T2 allele of the PROGINS polymorphism were found between patients with endometriosis and a history of obstetric complications (infertility, MP) and healthy women. A reliable association of severe forms of endometriosis and process prevalence in patients with T2\T2 genotype has been shown [8].

It is now known that there is a single integrating system of growth factors in the human body, which plays a major role in the processes of growth and differentiation of tissues, intercellular cooperation, hematopoiesis, angiogenesis, etc. [6]. The involvement of growth factors in the development of pregnancy (namely in the development of the mother-placenta-fetus system) is represented by a well-coordinated system of cellular reactions regulated by local mediators - cytokines and steroid hormones.

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

Disturbances in the formation of a complete chorionic vascular system play a major role in the pathogenesis of such frequent obstetric pathology as gestosis, placental insufficiency and MP [6,8,16,21]. It is known that the proliferation of vascular endothelial cells is provided by the whole complex of growth factors: vascular endothelial factor, transforming factor, insulin-like factor, tumor necrosis factor, etc. [6,8,16,21]

The role of growth factor gene polymorphism in MP is only beginning to be studied. 4 polymorphic variants are known in the gene of vascular endothelial growth factor (VEGF): 2578 C/A, 1154 G/A, 634 G/C, 936 C/T. Polymorphism in 1154 G/A of VEGF gene is represented by two alleles: G-normal and A-mutant. In homozygotes for allele A, blood VEGF level is significantly lower than in individuals with G\G genotype, indicating the effect of this polymorphism on VEGF gene expression [8,16,21].

It is known that maternal blood levels of growth factors are reduced in MP. For example, in women with spontaneous miscarriage or frozen pregnancy in the first trimester of pregnancy, serum VEGF concentration is 2-fold lower, and insulin-like growth factor-1 level is more than 4-fold lower than in normal pregnancy [6,8,16,21].

The frequency of the 1154A allele of the VEGF gene in women with a history of three or more spontaneous miscarriages was significantly higher than in the control group [396]. The association of the 936C/T polymorphism of the VEGF gene with the risk of PMP development was also established. Thus, C/T and T/T genotypes were diagnosed 1.5-fold more frequently in patients with habitual fetal loss than in normals.

Thus, the reduction or imbalance of growth factors in women with MP may be genetically determined. Study of polymorphism and peculiarities of the expression of genes for chorionic and placental growth factors is important to work out diagnostic tests for presymptomatic diagnostics and

prognosis of MP, and in future will make it possible to develop new pathogenetic therapy for this pathology.

However, given the compensatory abilities of the organism, the observed changes 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. But there is a complex homeostasis system in human body which has adaptive properties. Nevertheless, in the combination of functionally impaired alleles against the background of unfavorable (provoking) environmental factors, such polymorphisms may play an important role in pregnancy pathology and embryonic development disorders. Given the complexity of metabolic systems that determine the harmonious interaction between mother and fetus, functional impairment of many genes is realized during pregnancy.

Therefore, the possibility of early presymptomatic diagnosis of any obstetric pathology allows preventive treatment to begin before the clinical manifestations of the disease. The latter circumstance is particularly important to consider for patients in whom pathology has not yet developed, but there is a pronounced genetic predisposition to its development.

Recently, hyperhomocysteinemia, hyperprolactinemia, insulin resistance, obesity, unsatisfactory spermogram parameters are possible reasons for pregnancy termination. Extragenital diseases and socio-biological factors have a significant impact on the course of pregnancy [7].

According to various authors, in 5-20% of cases the causes of miscarriages cannot be determined by current diagnostic resources, so the diagnosis is formulated as a recurrent miscarriage of unclear etiology (idiopathic recurrent miscarriage) [7].

Finding out the causes of habitual pregnancy loss is extremely important from a practical point of view. Knowing the causes and understanding the pathogenesis of pregnancy termination allows a more successful pathogenetic treatment, otherwise it becomes symptomatic and often ineffective. [9, 10,12,16, 22, 23].

About 15% of women with pregnancy failure have abnormal anatomical structure of the uterus, which is the main cause of miscarriages. These anomalies can be divided into 3 categories: abnormalities of the normal process of uterine embryos fusion (anomaly of the Müllerian duct - intrauterine septum, bicornuate uterus, uterine doubling); abnormalities of uterine size or blood supply due to myoma, endometrial polyps; cervical function disorders. Currently, ultrasound, hysterosalpingography, hysteroscopy are used to make the diagnosis. Surgical treatment is most effective in the presence of an intrauterine septum, with specialists performing hysteroresectoscopy. The rate of subsequent miscarriages in these women is 10% compared to 90% before surgery.

In most women, uterine myoma does not result in decreased fertility and complications during pregnancy. Spontaneous miscarriage associated with myoma is due to the large size or location of the myoma node. Spontaneous miscarriage is most likely in the submucosal location of the uterine myoma. Large intramural myomatous nodes, leading to a narrowing of the uterine cavity and thus impairing blood flow at the implantation site of the fetus, can also be a cause of early pregnancy termination.

Ascherman syndrome is also a cause of spontaneous miscarriage. It is diagnosed by a hysterosalpingogram or hysteroscopy and treated by separating the intracavitary adhesions under visual inspection during hysteroscopy.

The leading place among the causes of NT in the second and third trimesters is occupied by isthmic-cecal insufficiency.' Its frequency varies from 5.2 to 34% depending on the structural changes of the cervix, the tactics of pregnancy management, and the number of premature births. Organic cervical ismico-cervical insufficiency (anatomic) develops as a result of traumatic lesions of the cervical ismical region due to ruptures during delivery, induced abortion, diathermic coagulation of erosions, and other surgeries. Functional ischemic-cesvical insufficiency develops as a rule during pregnancy in 40% of women with NS and is often related to infantilism and hormonal insufficiency; its development is usually associated with dysregulation of the contractile function of uterine muscles.

Surgical correction of isthmic-cesmic insufficiency by cervical suturing in the second trimester of pregnancy or pessary implantation gives an opportunity to prolong pregnancy.

Endocrine disorders account for 8-20% of the causes of pregnancy failure. The most significant of these are: luteal phase insufficiency (LPhI), hyperandrogenism, thyroid dysfunction, diabetes mellitus (23).

The most common cause of recurrent miscarriage is LPHI, which is the insufficient effect of progesterone on the endometrium. According to some authors (24), LPHI accounts for 5-40% of the etiology of habitual miscarriage. Normal implantation requires synchronization of ovulation with the "receptivity window" of the endometrium, the key role in the formation of which is played by progesterone. Clinically, a decrease in progesterone levels is expressed by a shortening of the luteal phase and is confirmed histologically. Luteal phase failure is heterogeneous in its etiology and pathogenesis, and may be due to hyperprolactinemia, weight deficiency, obesity, polycystic ovaries, primary hypothyroidism, chronic adnexitis, and genital endometriosis. It can also be observed in normogonadotropic normoprolactinemic ovarian insufficiency [23,24,25].

Hyperandrogenemia ranks second in the structure of hormonal disorders, accounting for 20-60% [13,]. Various forms of hyperandrogenism with predominant involvement of the adrenal glands, ovaries or both organs are manifestations of clinical polymorphism of a single pathology that depends on the duration and depth of the pathological process and has one root cause - disorders of hypothalamic-pituitary-adrenal-ovarian relationships at different stages of development of the female body [13,23]. The cause of MP is mainly sterile "non-classical" forms of hyperandrogenism, which are detected in some cases only during stress tests or pregnancy. The most frequent complication of pregnancy in women with hyperandrogenism is placental insufficiency (75-81.6% of cases) and premature termination of pregnancy. Hyperandrogenism often results in termination of pregnancy by a type of an uncompleted pregnancy in the first trimester or intrauterine fetal death.

According to some authors, with hyperandrogenism of any genesis, the most frequent pregnancy termination occurs in the first trimester as an undescended pregnancy, or an embryo. An increase in androgen levels leads, on the one hand, to fetal death directly, and on the other hand, to placental insufficiency. At later terms - 24-26-28-32 weeks, it is possible to develop severe placental dysfunction, RFDS, which in some cases leads to antenatal fetal death.

Thyroid disorders (such as hypothyroidism, autoimmune thyroiditis, diffuse toxic goiter) play a significant role in the pathogenesis of MP (4). The rate of early termination of pregnancy is increased in diabetes mellitus, obesity, and body weight deficiency. Mechanisms of pregnancy termination in these hormonal disorders are insufficient preparation of the endometrium for pregnancy, incomplete implantation of the fetus, increased myometrial excitability, primary placental insufficiency in the second trimester, and fetal growth disorders as a result of embryotoxic action of hyperglycemia.

Systemic endocrine diseases, such as diabetes mellitus and thyroid dysfunction are associated with pregnancy failure, but with adequate therapy, they do not increase the risk of termination.

The tendency to excessive blood clotting in women is one of the important causes of pregnancy failure. To diagnose clotting disorders, hemostasiogram, D-dimer, lupus anticoagulant, homocysteine, autoantibodies are examined.

According to some literature sources, autoimmune conditions may cause pregnancy failure in 10% of cases (5,19).

Currently, it is known that about 80% of all previously unexplained cases of recurrent pregnancy losses (after excluding genetic, hormonal causes) are associated with immune disorders. There are autoimmune and alloimmune disorders leading to habitual pregnancy failure.

In autoimmune processes, the maternal body's own tissues become the object of aggression of the immune system, i.e. there is a focus of the immune response against its own antigens. In this situation, the fetus suffers secondary damage to the maternal tissues.

As we know, the baby is half-foreign to the mother's body. This "foreignness" is a normal physiological phenomenon that triggers immunological reactions aimed at preserving the pregnancy. A clone of immune cells is formed, producing blocking antibodies.

Incompatibility between spouses according to HLA(humanleucocyteantigens)and the difference between the embryo and the maternal body is an important point necessary for preserving and carrying the pregnancy (2,3,26) In alloimmune disorders the immune response is directed against the fetal antigens of paternal origin that are foreign to the maternal body (2,13). Examples of alloimmune interactions are hemolytic disease in newborns due to Rh- or ABO-sensitization, AFS, as well as the presence of an increased number of common HLA antigens in spouses [19].

Autoimmune reactions are directed against the mother's own tissues, while the fetus suffers secondary to the resulting changes in the mother's condition. Examples of such interactions are antiphospholipid syndrome, diffusely toxic goiter, myasthenia gravis, autoimmune oophritis, systemic

lupus erythematosus and other diseases. 27% of patients with habitual non-fertility have autoimmune disorders. HLA system controls the interaction of all immunocompetent cells of the body, recognition of their own and foreign (including altered own) cells, triggering and implementation of the immune response and, in general, ensures the survival of humans as a species in conditions of exogenous and endogenous aggression [19].

Antiphospholipid syndrome (APS) is an autoimmune dysfunction. As is known, phospholipids are the main components of cell membranes, including placental cells. Antibodies to phospholipids are a diverse group of immunoglobulins that interact with many phospholipids of cell membranes. They can damage endothelial cells and the platelet membrane and inhibit prostacyclin synthesis (6).The result is an increase in platelet adhesion and a relative increase in thromboxane, which generally increases the incidence of thrombosis. The incidence of AFS in patients with pregnancy failure is 27-42% (), with untreated fetal/fetal death occurring in 90-95% of women with autoantibodies to phospholipids (6,8,21). Microthrombosis in the vessels of the developing chorion disrupts its function, resulting in embryonic death. Antibodies to cardiolipin in moderate to high titers have a negative impact on pregnancy outcome. Elevated autoantibody titers to DNA can cause inflammatory changes in the placenta and trigger a fetal rejection reaction. Beta-2-glycoprotein-1 inhibits the internal clotting pathway and is a cofactor for autoantibodies to cardiolipin.

RESULT AND DISCUSSION

The presence of antibodies to beta-2-glycoprotein-1 may be associated with the development of arterial and venous thrombosis, venous thromboembolism, thrombocytopenia, and pregnancy failure.

In autoimmune thyroiditis, there is an autoimmune response to the thyroglobulin protein. In the next stage of the disease, the mitochondria of the thyroid cells may be affected, accompanied by the appearance of antibodies to thyroid peroxidase and sometimes to microsomal thyroid antigen. Further, the levels of CD56+ and BI-cells increase, leading to the triggering of the pregnancy rejection reaction in autoimmune processes.

Lupus anticoagulant is an inhibitor of the antiplatelet system. Being present in the blood, it increases the clotting activity of the hemostasis system, which adversely affects the process of embryo implantation, the course of the entire pregnancy, and fetal development. Determination of D-dimer is a highly specific and sensitive marker of thrombosis. Its normal level allows us to rule out conditions accompanied by increased thrombosis with an accuracy of up to 98%.

To diagnose hyperhomocysteinemia, blood levels of homocysteine are determined, which is a product of metabolism of methionine, one of the eight essential amino acids of the body and has a pronounced toxic effect on the cell. Normally, homocysteine does not accumulate; it circulates in the blood and damages blood vessels, thereby increasing blood clotting and the formation of microthrombi in blood vessels. High concentrations of the active form of folic acid are needed to convert excess homocysteine to methionine.

Evidence of the adverse effect on pregnancy of persistent pathogenic and opportunistic microflora. Infectious diseases of pregnant women have an adverse effect on the fetus, both as a result of direct exposure to the pathogen and due to placental damage, inducing its dysfunction and secondary fetopathy (11,15). Viral diseases can lead to an embryo, miscarriage, spontaneous miscarriage, fetal malformations, intrauterine infection manifesting in the postnatal period.

Clinical studies have shown that one of the most common causes of pregnancy failure (MP) in women may be a urogenital bacterial-viral infection. Meanwhile, the etiological role of infection in MP is still debated. It has been suggested that infection is more likely to play a primary role in sporadic pregnancy termination than in habitual MP [6]. There is evidence that maternal infection may not interfere with the normal course of pregnancy and may not affect fetal development in the absence of significant changes in immune system parameters (3).According to current ideas, fetal survival depends on the complex cytokine regulation of maternal immune response, with a fluctuating balance between two types of cytokines during pregnancy, which can shift in either direction (3,10). In a normally developing pregnancy, the maternal immune system is more focused on the production of regulatory cytokines by type II T-helpers (IL-4, IL-10, etc.).

However, studies have shown that in women with MP the cytokine profile is focused on the production of pro-inflammatory cytokines by T-helper type I (TNF-α, IL-1, etc.) that can cause death of the fetoplacental unit due to excessive cytotoxic activation of NK-cells and phagocytic activity of

macrophages in the endometrium and decidual tissue [3].Currently, gene polymorphism of many cytokines has been identified.

Individual allelic variants of cytokine genes have been found to influence the rate of transcription, mRNA stability or quality, and the activity of the protein products they encode [2]. The relationship between cytokine genes and MP has been extensively studied. However, the relationship of cytokine genes with MP of infectious genesis remains understudied.

A large group of etiological factors includes acute and chronic maternal infectious diseases [11,14], local genital lesions caused by bacterial flora, mycoplasmas, chlamydia, ureaplasmas, gonococci, group B streptococci, toxoplasmas, listeria, viruses and fungi [11,14]. A characteristic feature of urogenital infections in modern conditions is their frequent associations. In the presence of genital infection, pregnancy can be terminated both early and late [13]. According to many authors, 50% of women with threatened pregnancies have cervical erosions, cervicitis, combined with colpitis [17]. Cervical inflammatory diseases in pregnant women may result in cervical mucus barrier failure and the spread of infection to the endometrium and fetal egg, with adverse outcomes for the developing fetus [17,22]. M. hominis and U. Urealyticum. These data are directly related to the fact that patients with recurrent miscarriages more often undergo intrauterine interventions, which contributes to the entry of these microorganisms from the cervix into the uterine cavity.

By activating cytokines and free radicals, any infection can have a direct cytotoxic effect, which contributes to pregnancy termination in both the first and second trimesters. Toxic products produced by microorganisms may damage the integrity of fetal membranes and lead to their premature rupture.

Viral infections deserve special attention (herpes, cytomegaly, adenovirus, rubella, mumps and others), whose pathogens penetrate the placental barrier and actively reproduce in the placenta, damaging it and causing intrauterine infection of the fetus [22,25]. Recent studies have shown that most women with recurrent miscarriages have a mixed persistent viral infection (coxsackievirus A, coxsackievirus B, enterovirus 68-71, cytomegalovirus, herpes simplex virus) combined with 2-3 or more persistent anaerobic and aerobic bacteria [18]. Viral infection leads to immune system and hemostasis disorders, inducing fetal rejection [13].

There was a high frequency of opportunistic genital infections in women with recurrent miscarriages, caused by opportunistic micro¬organisms and saprophytes, which is a kind of marker of immunocompetence deficits [11,15,17].

Women with a history of recurrent miscarriages, chronic mixed viral infection and autoimmune processes have an inter-feron deficiency condition [11]. A profound depression of cellular immunity reactions is observed in patients with a frozen pregnancy, which prevents the rejection of the fetal-placental complex [17].

The most frequent combined causes of MP are neuroendocrine disorders, traumatic endometrial injuries and urogenital infection, which play a determining role in the formation of endometrial morphofunctional incompleteness [9,11,15,17].

Inflammatory diseases of tonsils, pharynx, urinary organs and asymptomatic bacteriuria play a certain role in MP. Gestational pyelonephritis occurring against the background of altered immunological reactivity of the pregnant organism causes abnormalities in the feto-placental system and contributes to premature termination of pregnancy. In every third pregnant woman chronic pyelonephritis is exacerbated [13,15]. Urinary tract infection can lead to premature delivery, intrauterine infection of the fetus, placental insufficiency, fetal retardation [13].

At least 50% of diagnosed pregnancies sporadically terminated in the first trimester are combined with chromosomal abnormalities (2). Genetic abnormalities account for 3-6% of the causes of pregnancy failure in women with a history of three or more miscarriages. Apparently, this can be explained by the randomness of the mutations, which accounts for the rare recurrence of this pathology. Thus, triploidy due to the non-dissemination of chromosomes during spermatogenesis leads to complete or partial vesicle shedding with proliferation of the trophoblast; trisomy. X-monosomy, triploidy due to non-discrepancy in ovogenesis leads to miscarriage with damage to the trophoblast. In a recurrent failed pregnancy, the altered chromosomal set of the embryo may be due to abnormal parental karyotype, occurring in 7% of married couples.

Chromosomal aberrations in human embryos may be caused by a variety of chemical (mutagens), physical (irradiation, temperature shock) and biological (viral infections) factors. Damaging factors may be of exogenous origin (most mutagens of any etiology) or result from metabolic

errors, functional disorders of genes deactivating toxic metabolites (free radicals, peroxide compounds and others) or DNA repair genes, stress or hormonal homeostasis disorders [2,3,27]. Among exogenous factors we consider smoking, various chemical and medicinal preparations. Among endogenous factors, autoimmune thyroiditis and diabetes mellitus are the most prominent [4].

Maternal age and heterozygous carrier of chromosomal rearrangements (translocations, inversions) by one of the parents are generally recognized factors provoking the formation of genetically uMPalanced gametes and zygotes in humans [2,3,27].

CONCLUSION

Factors influencing the occurrence of chromosomal anomalies are often found to be familial in nature. In families with normal karyotypes that have a fetus or child with a chromosomal imbalance, the recurrent risk of chromosomal abnormalities in the fetus may be increased.

Thus, adequate examination and identification of the causes of pregnancy failure in each case allows the development of optimal methods of prevention and rational preparation of couples with a history of reproductive losses for subsequent pregnancy and to achieve its successful completion. Comprehensive drug therapy in a number of cases makes it possible to achieve pregnancy termination. However, there remains a category of patients resistant to drug therapy, which dictates the need for more extensive screening followed by pre-pregnancy preparation.

Further research is needed to determine the role of genetic polymorphisms in predisposition to habitual pregnancy loss. Identification of individual causative factors and pathogenetic mechanisms underlying habitual pregnancy loss will allow future prediction of gestational complications and timely preventive measures based on an individualized approach to therapy.

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