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FOLATE CYCLE DRUGS IN THE COMPLEX PREVENTIVE THERAPY FOR THE MISCARRIAGE

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120 women of reproductive age were examined. Alleles of folate-related enzyme genes, the content of folic acid, cyanocobalamin, vitamins B_1, B_6 in the blood were determined. Prevention of miscarriage was based on preconception training of men and women (spouses). The pre-conceptual examination plan included a thorough study of the anamnesis, including family history; laboratory determination of folic acid, vitamins B_{12}, B_1, B_6 in the blood of future parents (both woman and man). Decreased vitamin content or their level at the lower limit of normal was an indication for determining the folate-related enzyme genes (*MTHFR: 1298A/C; 677C/T, MTR: 2756A/G*, *MTRR: 66A/G*). Given the high (78.1 %) incidence of carriers of "functionally attenuated" (polymorphic) genes of folate cycle enzymes, both expectant parents were prescribed modern complexes of vitamins, microelements and amino acids containing Metafolin at the stage of preconception preparation 3-4 months before fertilization and during pregnancy according to the trimesters of gestation. Clinical and laboratory approach to the correction of vitamins, macro-, microelements, amino acids based on laboratory assessment of hereditary impairment of specific enzymes and by prescribing personalized therapy had a positive result in 57 (95.0 %) patients, which confirms its effectiveness.

Key words: folic acid, vitamins B_{12}, B_1, B_6, alleles of folate-related enzyme genes, prevention of miscarriage.

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ПРОФІЛАКТИКА НЕВИНОШУВАННЯ ВАГІТНОСТІ ШЛЯХОМ ЗАСТОСУВАННЯ ФОЛАТІВ У КОМПЛЕКСНІЙ ТЕРАПІЇ

Обстежено 120 жінок репродуктивного віку. Визначено алелі генів ферментів фолатного циклу, вміст фолієвої кислоти, ціанокобаламіну, вітамінів B_1, B_6 в крові. Профілактика невиношування вагітності базувалась на преконцепційній підготовці чоловіка та жінки (подружжя). До плану обстеження в межах преконцепційної підготовки включалось ретельне вивчення анамнезу, в тому числі сімейного; лабораторне визначення вмісту фолієвої кислоти, вітамінів B_{12}, B_1, B_6 у крові майбутніх батьків (і жінки, і чоловіка). Знижений вміст вітамінів або їхній рівень на нижній межі норми був показанням до визначення генів ферментів фолатного циклу (*MTHFR: 1298A/C; 677C/T, MTR: 2756A/G, MTRR: 66A/G*). Враховуючи високу (78,1 %) частоту зустрічаємості носіїв «функціонально ослаблених» (поліморфних) генів ферментів фолатного циклу, обом майбутнім батькам на етапі преконцепційної підготовки призначались сучасні вітамінно-мікроелементні-амінокислотні комплекси, що містять Метафолін, за 3–4 місяців до запліднення та під час вагітності за триместрами гестації. Клініко-лабораторний підхід до корекції вмісту вітамінів, макро-, мікроелементів, амінокислот на підставі лабораторної оцінки спадкового порушення активності специфічних ферментів та шляхом призначення персонофікованої терапії мав позитивний результат у 57 (95,0 %) обстежуваних, що підтверджує його ефективність.

Ключові слова: фолієва кислота, вітаміни B_{12}, B_1, B_6, алелі генів ферментів фолатного циклу, профілактика невиношування.

The study is a fragment of the research project "The role of chronic infection of the uterus and lower genital tract in the formation of obstetric and gynecological pathology", state registration No. 0117U005276.

The prevention of miscarriages (PM) is one of the most important tasks of medicine today. The urgency of the problem lies in the high frequency of this pathology and the negative consequences for the woman's body. Premature termination of pregnancy at different times can contribute to the occurrence of gynecological (cervical incompetence, infectious processes of the uterus, cervix and uterine appendages, vagina, etc.) and somatic (anemia, neuroses, vascular diseases, etc.) pathologies. In addition, reproductive loss is a severe psychological trauma for a woman, her husband, and family members. Primary premature termination of pregnancy, habitual miscarriage (2 or more times) by pathogenetic mechanism is a

consequence of pathological processes that occur in response to complex metabolic disorders in the bodies of future parents [3–4, 7–8].

One of the main causes of PM, as a multifactorial pathologies in early pregnancy are chromosomal aberrations and various genetic factors. The existence of "functionally attenuated" alleles of genes of hereditary predisposition to PM emphasizes the need to identify alleles of genes "candidates" associated with the risk of PM at the stage of preconception preparation for pregnancy [1–2, 11].

The pathogenetic mechanism of PM as a pathology of multifactorial nature is quite complex. The genetic component, gestational age, directly damaging factor, tissue destruction, etc. are important in the occurrence of pathology of the embryo, chorion, and placenta. Embryo development in the embryonic period depends on genetic heredity, internal (enzyme systems, hormones, etc.) and external (negative environmental factors) epigenetic factors [2, 5–6, 9]. These factors are interdependent in their action. There is almost no single isolated factor, because in the body all metabolic processes are interconnected by the mechanism of action of various substances and their breakdown products. For example, citrate and folate cycles, liver and kidney functions, etc. [3, 10, 12]. All of the above explains the constant search by scientists for new and improvement of existing diagnostic, preventive, and therapeutic measures to prevent PM. The expediency of a personalized approach to preventing premature termination of pregnancy by correcting the content of biologically active substances in the body of women and men: folate, trace elements, vitamins – antioxidants, amino acids, etc. is discussed.

The purpose of the study was to increase the effectiveness of complex personalized prevention of PM in women with deficiency of B vitamins, carriers of polymorphic alleles of folate-related enzyme genes using modern diagnostic and preventive measures.

Materials and methods. 180 people were examined: among them, 120 women aged 18 to 35 years before and during pregnancy and 60 men. All the women were primigravida. The examined patients distributed as follows:

– Main group A – 60 women and 60 of their men, who at the stage of pre-conception preparation showed signs of violation of the content of folate cycle vitamins and the presence of polymorphic alleles of folate-related enzyme genes; they had no signs of hyperthyroidism. In this group, spouses received nutritional support with folate cycle drugs during preconception training, and women – during pregnancy;

– Comparison group B – 60 women, who also showed signs of impaired folate cycle vitamins and the presence of polymorphic alleles of folate-related enzyme genes, but who refused nutritional support with folate cycle drugs and, if necessary, prescribed drugs regulated by Order No. 417 of the Ministry of Health Of Ukraine from 15.07.2011.

Clinical examination of patients was performed in the Odessa Maternity Hospital No. 1 and laboratory examination – in the Synevo laboratory.

The level of folic acid and cyanocobalamin was determined by immunochemical method; the content of vitamins B_1, B_6 – by liquid chromatography; alleles of the genes of methylenetetrahydrofolate reductase (*MTHFR: 1298A/C; 677C/T*), methionine synthase (*MTR: 2756A/G*), methionine synthase reductase (*MTRR: 66A/G*) – by polymerase chain reaction (PCR).

In order to correct the content of vitamins, macro-, microelements, amino acids, stabilization of metabolic processes, the main group (women before and during pregnancy, men at the stage of preconception preparation) was prescribed micronutrients in the diet. Micronutrients – are products containing natural folate in daily doses; vitamin complexes containing 400 mcg of folate and 200 mcg of folic acid, calcium– *L* – methylfolate (*Metafolin* – equivalent to 200 mcg of folic acid), docosahexaenoic acid (200 mg) and vitamins and vitamin-like compounds of group B, vitamins C and E. Metafolin is a biologically active form of folate based on folic acid metabolism – *L-5-MTHF*, which is characterized by the presence of calcium ions (Ca^{+2}) and actually L-*5-MTHF* [6].

The study was performed in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the Local Ethics Committee for all participants. Information consent of patients was obtained for the study.

Statistical processing was performed using the software package Statistica 6.0 (StatSoft Inc., USA). The analysis of parameters relative to the normality of the distribution was performed using the Shapiro–Wilk test. Descriptive statistics for quantitative indexes were presented as the arithmetic mean and standard error of the mean – M±m, and under conditions of distribution other than normal – as the median and interquartile range Me (Q25–Q75). Qualitative indices are provided in the form of absolute quantities and percentages. Comparison of qualitative indices was carried out according to the $\chi 2$ criterion. All statistical tests were bilateral, the level of $p<0.05$ was considered significant.

Results of the study and their discussion. According to the results of retrospective analysis of medical records of the patients, the obstetric and gynecological anamnesis was analyzed, the indices of

prospective examination were studied, including the frequency of extragenital diseases, gynecological pathology, for which no significant difference was found between groups. Of the 120 (100 %) women examined, 76 (63.3 %) had cardiovascular disease (CVD); 56 (46.7 %) – pathology of the thyroid gland; 44 (36.7 %) – diseases of the hepatobiliary system, gastrointestinal tract, chronic constipation and 32 (26.7 %) – diseases of the genitourinary system (GUS). 16 (13.3 %) women suffered from iron deficiency anemia before pregnancy. Menstrual disorders were indicated by 24 (20.0 %) women, and primary infertility was indicated by 8 (6.7 %) women. Among the 60 men examined, 49 (65 %) had CVD and 28 (46.7 %) had GUS diseases. More than 70 % (126) of women and men were long-term smokers.

Analysis of laboratory results showed that at the stage of pre–conception preparation for pregnancy, 13 (21.6 %) out of 60 women in the main group had folic acid content at the lower limit of reference values (4.6–5.0 ng/mL), and 17 (28.3 %) – within the lower median reference values (5.1– 6.6 ng/mL). In 29 (48.3 %) women, cyanocobalamin levels were at the lower limit of the reference values (191.0–200.0 pg/mL). In 13 (21.7 %) men in Group A, folic acid levels were at the lower limit of the reference values, and in 18 (30.0 %) – within the lower median reference values. In 20 (33.3 %) examined men, the level of cyanocobalamin was at the lower limit of the reference values.

Combined subclinical deficiency of vitamin B_1 (40.5–48.9 mcg/L) (reference values >49.0 mcg/L) and vitamin B_6 (7.6–8.1 mcg/L) (reference values 8.2–27.2 mcg/L) was found in 31 (51.7 %) women of Group A and 28 (46.7 %) men.

In the first trimester (10–11 weeks of pregnancy), in 37 (61.7 %) women of the main group who underwent the prescribed pre-conception training, the content of folic acid in the blood ranged from 11.2 to 18.5 ng/mL, cyanocobalamin – from 491.0 to 663.0 pg/mL, vitamin B_1 – 49.0–76.7 mcg/L, B_6 – 8.2–27.2 mcg/L. While in the comparison group at the same time, the content of folic acid in the range of 7-9 ng/mL was in 29 (48.3 %) women, vitamin B_{12} in the range of 201.5–302.7 ng/mL – in 23 (38.3 %) patients, vitamin B_1 – 40.5–48.9 mcg/L – in 25 (41.7 %) pregnant women, vitamin B_6 – 7.6–11.4 mcg/L in 24 (40.0 %) women. Significant differences between the presented indices between group A and group B took place during the second and third trimesters of pregnancy.

Combined deficiency of B vitamins (folic acid, vitamin B_1, vitamin B_6, cyanocobalamin) was found in 92 (76.7 %) of the examined women in both groups.

The results of determination and characterization of alleles of folate-related enzyme genes in 60 men and 60 women of the main group are presented in table 1.

Table 1

Characteristics of alleles of folate-related enzyme genes in the main group of patients

Genes	Polymorphism	Alleles							
		Homozygous				Heterozygous			
		Men, n=60		Women, n=60		Men, n=60		Women, n=60	
		abs.	**%**	**abs.**	**%**	**abs.**	**%**	**abs.**	**%**
MTHFR (methylene tetrahydro folate reductase)	*1298A/C*	11	18.3	13	21.7	31	51.7	34	56.7
MTHFR (methylene tetrahydro folate reductase)	*677C/T*	10	16.7	12	20.0	29	48.3	35	58.3
MTR (methionine synthase)	*2756A>G*	13	21.7	11	18.3	15	25.0	31	51.7
MTRR (methionine synthase reductase)	*66A>G*	9	15.0	8	13.3	27	45.0	37	61.7

In main group A, polymorphic alleles (homozygous, heterozygous) (*MTHFR 1298A/C*) were found in 47 (78.3 %) women and 44 (73.3 %) men, (*MTHFR 677C/T*) – in 47 (78.3 %) women and 39 (65.0 %) men, *MTR (2756A>G*) – in 42 (70.0 %) women and 28 (46.7 %) men, *MTRR (66A>G)* – in 46 (76.7 %) women and in 36 (60.0 %) men. That is, the presence of "functionally attenuated" genes of folate cycle enzymes in the body of future parents (men and women) in 78.1 % of cases against the background of combined subclinical deficiency of folate cycle vitamins may pose a risk of vascular disorders, disorders of chorionic embryonic, fetoplacental complex and direct abortion [2].

The results of determination and characterization of alleles of folate-related enzyme genes in 60 women of the comparison group are presented in table 2.

In the comparison group, polymorphic heterozygous alleles of folate-related enzyme genes were detected in 56.4 % of cases, which did not make a significant difference between the indices of the main group and the comparison group.

In the dynamics of monitoring the course of pregnancy, a comparative analysis between the observation groups showed that the content of the studied vitamins at 18–19 and 36–37 weeks of pregnancy was significantly lower in 28 (46.6 %) women in the comparison group, against 5 (8.3 %) women of the

main group who received a drug containing Metafolin. Clinical and laboratory approach to the correction of vitamins, macro-, microelements, amino acids based on laboratory assessment (PCR) of hereditary impairment of specific enzymes and by prescribing personalized therapy had a positive result in 57 (95.0 %) patients, which confirms its effectiveness.

Table 2

Characteristics of alleles of folate-related enzyme genes in women of the comparison group, n=60

Genes	Polymorphism	Homozygous alleles		Heterozygous alleles	
		abs.	**%**	**abs.**	**%**
MTHFR (methylenetetrahydrofolate reductase)	1298A/C	12	20.0	36	60.0
MTHFR (methylenetetrahydrofolate reductase)	677C/T	14	23.3	34	56.7
MTR (methionine synthase)	2756A>G	10	16.7	32	53.3
MTRR (methionine synthase reductase)	66A>G	9	15.0	33	55.0

We have developed and proposed personalized prevention of PM, which consists of four stages:

Stage I – examination, which includes laboratory determination of genes of folate cycle enzymes (*MTHFR: 1298A/C; 677C/T,* MTR: *2756A/G, MTRR: 66A/G)*, levels of folic acid, cyanocobalamin, vitamins B_1, B_6; determination of risk groups for hereditary predisposition to miscarriage from among the carriers of "functionally attenuated" polymorphic genes in the body of future parents (risk “low”, “medium”, “high”);

Stage II - preparatory, which includes correction of the content in the body of future parents (both men and women) of folic acid, cyanocobalamin, vitamins B_1, B_6, deficiency of which has laboratory confirmation, and the use of drugs containing Metafolin;

Stage III – pregnancy planning;

Stage IV – control of levels of folic acid, vitamins B_1, B_6, B_{12} in the blood of women in groups of "high" risk of miscarriage at 9–11, 19–20, 34–36 weeks and the use of nutrient therapy, complexes of vitamins, macro-and micronutrients containing Metafolin and docosahexaenoic acid.

The proposed therapy for women of the main group contributed to a significant decrease in the frequency (compared with women in the comparison group) of the occurrence of retrochorial hematoma – by 7 times, spontaneous early miscarriage – by 4 times, the risk of miscarriage (early, late) (O20.0) – by 3.1 times, the threat of premature birth (O60) – by 3.2 times, placental dysfunction (O43.8) – by 3.5 times, fetal growth retardation syndrome (O36.5) – by 3.0 times, gestational anemia (D50–D64) – 4.1 times, gestational pyelonephritis (O23.0) – by 3.2 times, preeclampsia (O14) – by 2.5 times ($p<0.001$) (fig. 1).

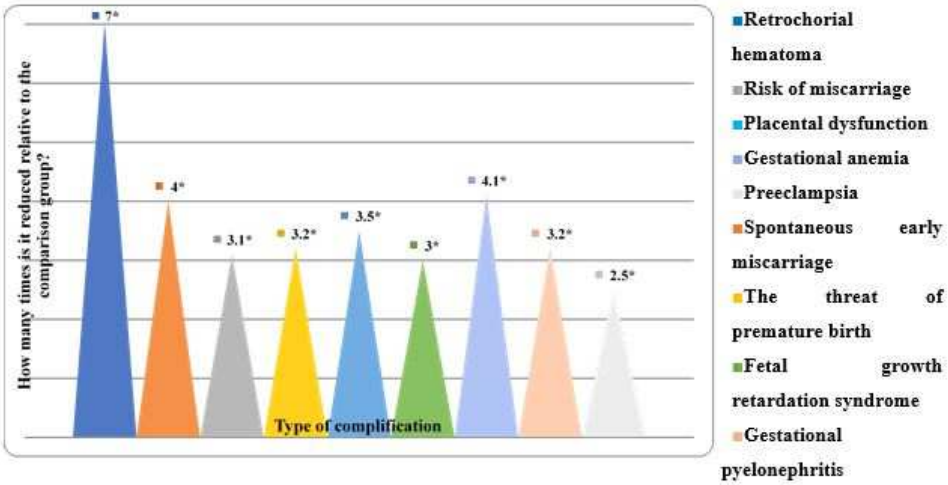

Fig. 1. The effectiveness of the proposed therapy in the main group compared with the comparison group (* – $p<0.05$)

Late spontaneous miscarriage, abortion, premature birth, premature placental abruption were not observed in the group receiving the proposed therapy.

The presence of “functionally attenuated” (polymorphic) alleles of folate-related enzyme genes may indicate a violation of the folate cycle (folic acid cycle, conversion of the amino acid homocysteine to methionine). The reduced form of folic acid (tetrahydrofolic acid) performs the functions of a coenzyme in the metabolism of a number of amino acids, including methionine [6, 10]. Appropriate enzymes, including 5-methyltetrahydrofolate, dihydrofolate reductase, metabolize folic acid. The corresponding genes of folate metabolism control the completeness of the enzyme system. In the presence of “functionally attenuated” (polymorphic) these genes, synthetic folic acid may not be absorbed by the body. The form of

vitamin B_9 (L–methylfolate), which is able to participate in DNA synthesis, cell replication, and methylation, has biological activity [6, 11].

Laboratory control of the content of vitamins and vitamin-like compounds of group B is of fundamental practical importance at the stage of preconception preparation for pregnancy and during trimesters of gestation. The practical significance of these indices is especially important in carriers of polymorphic alleles of folate-related enzyme genes. The definition of "functionally attenuated" genes of folate cycle enzymes makes it possible to classify such patients as "at risk" of gestational complications, including miscarriage and congenital malformations of the fetus and others.

The use of folate drugs in the complex prevention of PM has a reasonable practical significance. Folates are part of enzymes and coenzymes [5, 12]. The key point in the folate cycle is the synthesis of the amino acid methionine from the amino acid homocysteine. Metabolic disorders of the folate cycle are realized by hyperhomocysteinemia, which leads to endothelial dysfunction, DNA hypermethylation, and chromosome separation disorders, which contributes to chorionic/placental abruption, placental dysfunction, premature termination of pregnancy [2, 5, 7].

The data obtained indicate the need to perform clinical and laboratory examination of women "at risk" in the daily practice of obstetricians and gynecologists in order to identify hereditary predisposition to miscarriage and prescribe personalized preventive, therapeutic measures.

Our nutritional and drug therapy (vitamin complexes containing folate before pregnancy and during gestation) helped to stabilize the content of folic acid, cyanocobalamin, vitamins B_1, B_6, coagulation parameters, liver tests, general blood tests. This normalization of the folate cycle prevented hyperhomocysteinemia, vascular disorders and, most importantly, the occurrence of miscarriage.

The presented results of our study were consistent with the clinical assessment of the somatic state of women, chorioembryonic, fetoplacental complex by trimesters of gestation, which reliably confirmed the positive significance of the proposed personalized, pathogenetically sound approach to the prevention of miscarriage and other gestational complications.

Conclusion

Preconception training for women at risk of miscarriage should be started 3–4 months before pregnancy, which allows for a full examination of both future parents and, if necessary, to carry out appropriate preventive treatment.

The pre-conceptual examination plan included a thorough study of the anamnesis, including family history; laboratory determination of folic acid, vitamins B_{12}, B_1, B_6 in the blood of future parents (both woman and man). Decreased vitamin content or their level at the lower limit of normal was an indication for determining the folate-related enzyme genes (*MTHFR: 1298A/C; 677C/T, MTR: 2756A/G, MTRR: 66A/G*).

Given the high (78.1 %) frequency of carriers of "functionally attenuated" (polymorphic) genes of folate cycle enzymes, both expectant parents were prescribed modern complexes of vitamins, microelements and amino acids containing Metafolin at the stage of preconception preparation 3–4 months before fertilization and repeat such cycles during pregnancy according to the trimesters of gestation.

Prospects for further research are aimed at predicting the development of other obstetric and perinatal complications in women-carriers of polymorphic alleles of folate-related genes.

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SYNDROMAL COMORBIDITY IN PATIENTS WITH NON-CHEMICAL ADDICTION

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The paper presents the results of the study of the comorbid pathology characteristics in conditions of distress in patients with non-chemical addiction. 76 male Internally displaced persons were examined who sought psychiatric help due to the presence of polymorphic symptoms, the main manifestations of which were affective disorders with panic attacks, sleep disturbances and suicidal thoughts. A four-dimensional questionnaire to assess distress, depression, anxiety, and somatization (The Four-Dimensional Symptom Questionnaire – 4DSQ) was used. A high level of depression, anxiety and somatization in patients with non-chemical addiction does not depend on the severity of distress; the effect of distress is a highly pathogenic factor for patients with non-chemical addiction, which acts as a trigger. In the structure of clinical manifestations, depressive dominates the degree of severity and prevalence and anxiety disorders, which augment the appearance of somatic symptoms, cause dysfunction of the autonomic nervous system and determine the abundance and diversity of somatic pathology.

Key words: male adolescents and juvenile, non-chemical addictions, comorbid pathology.

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СИНДРОМАЛЬНА КОМОРБІДНІСТЬ У ПАЦІЄНТІВ З НЕХІМІЧНОЮ АДИКЦІЄЮ

В роботі представлені результати дослідження особливостей коморбідної патології в умовах дистресу у пацієнтів з нехімічною адикцією. Було обстежено 76 пацієнтів вимушених переселенців чоловічої статі, які звернулися за психіатричною допомогою в зв'язку з наявністю у них поліморфної симптоматики, основні прояви якої були афективні порушення з нападами паніки, порушення сну і наявність суїцидальних думок. Був використаний чотиривимірний опитувальник для оцінки дистресу, депресії, тривоги і соматизації (The Four-Dimensional Symptom Questionnaire – 4DSQ). Високий рівень депресії, тривоги і соматизації у пацієнтів з нехімічною адикцією не залежить від ступеня вираженості дистресу; вплив дистресу є для хворих з нехімічною адикцією високопатогенним фактором, який виконує роль тригера. У структурі клінічних проявів за ступенем вираженості і поширеності переважають депресивні і тривожні розлади, які аугментують появу соматичних симптомів, викликають порушення функціонування вегетативної нервової системи і обумовлюють велику кількість і різноманітність соматичної патології.

Ключові слова: підлітки і юнаки чоловічої статі, нехімічні адикції, коморбідна патологія.

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The current level of society development is characterized by the widespread use of information and computer technology, which generates new types of entertainment. Addiction to online games has been recognized by scientists as a mental illness and included in a previous version of ICD-11 [2]. Internet addictions can also be attributed to the group of technological addictions − non-chemical (behavioral) dependencies that are implemented using modern technology [3]. Internet addiction is most often manifested in a young age among adolescents and young people, which significantly complicates their socialization and impedes integration into society [4].

A large number of studies have been conducted on non-chemical addictions, the publications present the results of the analysis of the mental health of adolescents with computer addiction, study gender characteristics, the role of family and social factors [7, 8, 12].