винятком нижніх других малих кутніх зубів) достовірно більші або мають тенденцію до більших значень, ніж у дівчат із широким обличчям; а також в юнаків із широким обличчям більшість розмірів ширини зубів на рівні анатомічної шийки у мезіодистальному напрямку (за винятком нижніх центральних та латеральних різців) достовірно більші, ніж у дівчат із широким обличчям. При порівнянні розбіжностей комп'ютерно-томографічних розмірів ширини коронок зубів та ширини зубів на рівні анатомічної шийки у мезіодистальному напрямку між дівчатами із широким та дуже широким обличчям встановлено лише достовірно більше значення ширини верхніх центральних різців на рівні анатомічної шийки у дівчат із дуже широким обличчям.

Ключові слова: юнаки, дівчата, тип обличчя, комп'ютернатомографія, мезіодистальні розміри зубів, фізіологічний прикус, статеві відмінності.

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мезиодистальном направлении (за исключением нижних вторых малых коренных зубов) достоверно большие или имеют тенденцию к большим значениям, чем у девушек с широким лицом; а также у юношей с широким лицом большинство размеров ширины зубов на уровне анатомической шейки в мезиодистальном направлении (за исключением нижних центральных и латеральных резцов) достоверно большие, чем у девушек с широким лицом. При сравнении различий компьютерно-томографических размеров ширины коронок зубов и ширины зубов на уровне анатомической шейки в мезиодистальном направлении между девушками с широким и очень широким лицом установлено только достоверно большее значение ширины верхних центральных резцов на уровне анатомической шейки у девушек с очень широким лицом.

Ключевые слова: юноши, девушки, тип лица, компьютерная томография, мезиодистальные размеры зубов, физиологический прикус, половые различия.

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MEDICO-GENETIC DIAGNOSIS OF HEREDITARY PREDISPOSITION TO NONCARRYING OF PREGNANCY AND REPRODUCTIVE LOSSES

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The analysis of genetic models (gene grids) of genes associated with the risk for noncarrying of pregnancy: 2 collagen (COL2A1 6846C/A), plasminogen activator inhibitor-1 (RAI-1 PLANH1), superoxide dismutase (SOD1 7958 G/A), glutathione S-transferase (GSTμ1), N-acetyltransferase 2 (NAT2) has been carried out in *327 women.* Their **r**ole in reproductive losses has been shown.

Keywords: medicogenetic diagnosis, hereditary predisposition, noncarrying of pregnancy, reproductive losses.

The research study subject is "The Role of Chronic infection of uterus and the lower sections of the genital tract in the formation of obstetric and gynecological pathology" (state registration number 0117U005276).

Noncarrying of pregnancy is a pathological process in the maternal body that occurs in response to the implantation and development of the fertilized egg, which contains not only the maternal but also paternal genetic information [1,3]. In the structure of reproductive losses common miscarriage accounts for about 25%. The risk of fetal loss accounts for 13-17%, 36-38% and 40-45% after the first miscarriage, the second one and after three miscarriages, respectively [2].

Various genetic factors (chromosomal aberrations, genetic mutations, genetic predisposition) are the major causes of noncarrying of pregnancy as the multifactorial pathology at the early terms. Early spontaneous abortion is interpreted as "an evolutionary mechanism for elimination of defective offspring" [4].

Reproductive losses at the early stages of pregnancy are determined by the whole group of genes: type 2 collagen (COL2A1 6846C/A), plasminogen activator inhibitor-1 (RAI-1 PLANH1), superoxide dismutase (SOD1 7958 G/A), glutathione S-transferase (GSTμ1), N-acetyltransferase 2 (NAT2) and others [1,3]. The low level of genetic monitoring, inadequately active predictions of gestational complications are considered as the major components of the problem for noncarrying and prevention of obstetric perinatal complications [2,6]. Identification of the genetic polymorphism associated with obstetric perinatal complications enables to establish a hereditary predisposition to reproductive losses [5].

The purpose of the study was to show the role of genetic polymorphism of the genes predisposed to obstetric perinatal complications [type 2 collagen (COL2A1 6846C/A), plasminogen activator inhibitor-1 (RAI-1 PLANH1), superoxide dismutase (SOD1 7958 G/A), glutathione S-transferase (GSTμ1), N-acetyltransferase 2 (NAT2)] in the reproductive losses of the multifactorial nature.

Material and methods. 123 women have undergone screening genetic testing in the outpatient and hospital conditions for the possibilities of noncarrying of pregnancy and the risk for development of other obstetric perinatal complications. Among them 21 pregnant women with normal pregnancy, childbirth, postpartum period, who gave birth to healthy babies (Group I; the controls) have been tested.

102 women with consecutive pregnancy from Group II (risk group) have been tested at the early terms of gestation. The risk group regarding the problems of noncarrying and obstetric perinatal complications has been formed considering the reproductive losses and obstetric perinatal complications in the past history, the presence of epigenetic factors, diseases and conditions that occur involving connective tissue dysplasia, polymorphism of genes candidates, associated with the risk for obstetric-gynecologic pathology, deficiency of B vitamins, fertilization in the winter and spring seasons, taking drugs, homeopathic agents and dietary supplements, presence of signs of acute respiratory viral infection at the early stages of pregnancy, perinatal infections, vaginal bloody discharge at the early (before 8 weeks) stages of pregnancy.

PCR-method has been used to determine the genotypes of genes of type 2 collagen (COL2A1 6846C/A), plasminogen activator inhibitor-1 (RAI-1 PLANH1), superoxide dismutase (SOD1 7958 G/A), glutathione S-transferase (GSTμ1), N-acetyltransferase 2 (NAT2).

Results of the study and their discussion. Type 2 collagen is the most common protein of the connective tissue matrix. Several options for the (C/C, C/A, A/A) polymorphism, where the A-allele is incomplete, have been identified in the COL2A1 6846C/A gene. The increased expression of the COL2A1gene resulted in the presence of A-alleles, leading to occurrence of functionally incomplete homotrimeric collagen fibers. In the control Group I normal homozygous C/C genotypes have been found in 15 women (71,4%), homozygous polymorphic A/A genotypes have been found in 1 woman (4,8%) and heterozygous C/A genotypes have been found in 5 individuals (23,8%). The indices were within the population levels for the Caucasian race.

In Group II the frequency of the polymorphic homozygous C/C genotype accounted for 7 cases (6,9%), homozygous A/A genotype accounted for 59 cases (57,8%) ($p < 0.01$), heterozygous C/A genotype accounted for 36 cases (35,3%). In Group II the odds ratio (OR) of the probability of obstetric perinatal complications development constituted 1,5 and was within the confidence interval (CI-0.53-2.69; P=0,95). The resulting data confirm the risk for obstetric perinatal complications in pregnant women from Group II due to impairment of the processes of collagen formation in the form of undifferentiated connective tissue dysplasia due to the presence of COL2A1 6846C/A gene polymorphism and give evidence to the existence of the substantial conjugation of COL2A1 6846C/A gene polymorphism on the A/A and C/A alleles with the development of non-carrying and obstetric perinatal complications. Plasminogen Activator Inhibitor-1, PAI-1 prevents the fibrinolysis and is encoded by the PAI-1 PLANH1 675 5G/4G genome. The carriers of the 4G alleles show higher concentration of PAI-1than carriers of the 5G alleles, which leads to increased risk for placenta dysfunction and noncarrying of pregnancy.

In Group I the frequency of normal homozygous 5G/5G genotype accounted for 14 cases (66,7%), homozygous 4G/4G genotype accounted for 1 case (4,8%) and heterozygous 5G/4G genotype accounted for 6 cases (28,6%). The indices were within the population levels.

In Group II, the frequency of the polymorphic homozygous 4G/4G genotype accounted for 67 cases (65,7%), homozygous 5G/5G genotype accounted for 9 cases (8,8%) ($p<0,01$), and heterozygous 5G/4G genotype accounted for 26 cases (25,5%). In Group II the odds ratio (OR) of the probability of obstetric perinatal complications development constituted 2,0 and was within the confidence interval (CI) - 0,53 - 2,69; P=0,95.

Superoxide dismutase is encoded by the SOD1 7958 G/A gene, which polymorphism is represented by the homozygous G/G alleles, heterozygous G/A alleles, where the SOD1activity is within the population indices, and homozygous A/A option, where the SOD1activity dramatically decreased. In Group I the frequency of the polymorphic homozygous A/A genotype has been registered in 3 women (14,3%), and homozygous G/G genotype has been registered in 18 women (85,7%). In Group II, the frequency of the polymorphic A/A genotype detection accounted for 71 cases (69,6%), G/G genotype accounted for 20 cases (19,6%) ($p<0,01$), and G/A genotype accounted for 11 cases (10,8%). In Group II the odds ratio of the probability of obstetric perinatal complications development constituted 1,6 and was within the confidence interval (CI) - 0,53 - 2,19; P=0,95. The foregoing explains to some extent the inability of antioxidant protection and the risk for development of infectious processes on the genetic level in the observed women. Phase II detoxification enzymes are represented by the superfamily of glutathione-S-transferases (GST) and acetyltransferases (NAT).

The increased sensitivity to xenobiotics has been found in patients with GSTμ1enzyme gene deletion, since it leads to complete loss of enzyme function. Genetically determined activity of glutathione transferases affects the development of different forms of reproductive disorders.

In Group I the frequency of normal homozygous +/+ alleles has been found in 10 women (47,6%). Homozygous deletion alleles have been detected in 9 cases (42,9%) in controls. The indices were within the population values for the Caucasian race (42,2-52,3%).

In Group II the frequency of deletion homozygotes (0/0) accounted for 72,5% ($p<0,01$). The OR was 9,6. The probability for development of obstetric perinatal complications was within the confidence interval (CI) - 0,53 - 11,9; P=0,95. The resulting data confirm the risk for obstetric perinatal complications development as a result of the xenobiotics metabolism disorder in the phase II detoxification due to the presence of deletion genotype of the m1 (GST m1 0/0) glutathione-S-transferase and the existence of the substantial conjugation of GSTμ1 gene polymorphism on the 0/0 alleles with the presence of the complications.

N-acetyltransferase 2 belongs to the phase II detoxification xenobiotics. The R/R allele of rapid metabolism without mutations, S2 and S1slow acetylating alleles have been found in the gene, which encodes the enzyme. In Group I the NAT2*4 (R/R) allele of rapid metabolism without mutations, which encodes the enzyme of rapid acetylation accounted for 19,0%. Mutagenic slow acetylating homozygous (S/S) S1 allele and slow acetylating homozygous (S/S) S2 allele was detected in 28,6% of all cases each. In Group II the frequency of slow acetylating S2 allele accounted for 59,8%. The difference in indices is significant ($p<0,05$). The OR for S2 allele was 3,1.

Conclusions

1. The probability for the development of gestational complications with relation to the presence of polymorphic alleles of genes predisposed to noncarrying of pregnancy: 2 collagen (COL2A1 6846C/A), plasminogen activator inhibitor-1 (RAI-1 PLANH1), superoxide dismutase (SOD1 7958 G/A), glutathione S-transferase (GSTμ1), N-acetyltransferase 2 (NAT2) is within the confidence interval and associated with obstetric perinatal complications.
2. Identification of the presence of genetic polymorphism, associated with reproductive losses of multifactorial nature proves the hereditary predisposition to obstetric perinatal complications.
3. Herein studies can have the prognostic value at the stage of pregnancy planning.

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Реферати

МЕДИКО-ГЕНЕТИЧНА ДІАГНОСТИКА СПАДКОВОЇ СХИЛЬНОСТІ ДО НЕВИНОШУВАННЯ ВАГІТНОСТІ І РЕПРОДУКТИВНИХ ВТРАТ

Руденко І.В., Ліхачов В.К., Міщенко В.П., Голубенко М.Ю., Шиманська Я.В.

Проведено аналіз генетичних моделей (генні сітки) генів, асоційованих з ризиком невиношування вагітності: колагену 2 типу (COL2A1 6846C/A), інгібітора активаторів плазміногена-1 (PAI-1 PLANH1), супероксиддисмутази (SOD1 7958 G/A), глутатіон-S-трансферази (GSTμ1), N-ацетилтрансферази-2 (NAT2) у 327 жінок та показана їх роль у репродуктивних втратах.

Ключові слова: медико-генетична діагностика, спадкова схильність, невиношування вагітності, репродуктивні втрати.

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МЕДИКО-ГЕНЕТИЧЕСКАЯ ДИАГНОСТИКА НАСЛЕДСТВЕННОЙ СКЛОННОСТИ К НЕВЫНАШИВАНИЮ БЕРЕМЕННОСТИ И РЕПРОДУКТИВНЫМ ПОТЕРЯМ

Руденко И.В., Лихачев В.К., Мищенко В.П., Голубенко М.Ю., Шиманская Я.В.

Проведен анализ генетических моделей (генные сетки) генов, ассоциированных с риском невынашивания беременности: коллагена 2 типа (COL2A1 6846C/A), ингибитора активаторов плазминогена-1 (PAI-1 PLANH1), супероксиддисмутазы (SOD1 7958 G/A), глутатион-S-трансферазы (GSTμ1), N-ацетилтрансферазы-2 (NAT2) у 327 женщин и показана их роль в репродуктивных потерях.

Ключевые слова: медико-генетическая диагностика, наследственная склонность, невынашивание беременности, репродуктивные потери.

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