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ASSOCIATION BETWEEN POLYMORPHISMS IN HUMAN INTERLEUKIN-6 AND TUMOR NECROSIS FACTOR A GENES AND DEVELOPMENT OF PRETERM LABOR

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Sporadic miscarriage is mostly associated with infectious causes. Infectious agents on the background of the gestational immunomodulation realize the pathogenic effect by direct damaging effect and through the cytokine system. In this case, it is relevant to study the functioning of the immune system in pregnant women. The content of cytokines in the body is genetically determined. The study of allelic polymorphism of cytokine promoters allows us to simulate a possible response of the organism to the introduction of microorganisms.

The aim of this study was to investigate the relationship between single nucleotide polymorphisms (SNPs) of the interleukin-6 (IL-6) gene promoter and the tumor necrosis factor a (TNFa) gene promoter in Belorussian women.

Materials and Methods. The case group consisted of patients with a diagnosis of spontaneous preterm birth (before 37 weeks gestation). The control group comprised healthy women with the term labor (≥37weeks). All participants were at least 18 years old at enrollment. Upon admission to the delivery room, 5 ml of venous blood was drawn from each participant. Samples were collected in tubes containing ethylenediamine tetraacetic acid, immediately centrifuged to separate the buff coat containing polymorphonuclear cells, and frozen at - 20 °C for later DNA extraction. DNA was extracted from whole blood by ready set. SNPs in the human IL-6 and TNFa genes, respectively, were analyzed using the polymerase chain reaction-restriction fragment length polymorphism method. The polymorphisms are analyzed in the present study IL6 promoter −174 G>C and TNFa promoter – 308 A>G. To compare the two independent groups by variables the Mann-Whitney U test was used. Odds ratio events in the one group to the chances of the same event in another (OR) and 95% confidence interval for them (95% CI). Significance was established at $p<0,05$. Statistical analysis was performed using the program «MedCalc 10.2.0.0» (MedCalc, Mariakerke, Belgium).

Results. The frequency of the allelic variants of the IL-6(-174G/C) and TNFa(-308A/G) genes in the examined patients is presented in table 1.

Table 1 - Allelic variants of the genes IL-6(-174G/C) and TNFa(-308A/G) in women with preterm and term labor, n, p%, 95%CI_p

Genotype	Case group (N=50)	Control group (N=50)
IL-6(-174CC)/TNFa(-308GG)	9 (18%; 9-31)	3 (6%; 1-17)
IL-6(-174GC)/TNFa(-308GG)	26 (52%; 37-66)	27 (54%; 39-68)
IL-6(-174GG)/TNFa(-308GG)	10 (20%; 10-34)	11 (22%; 12-36)
IL-6(-174GC)/TNFa(-308AG)	2 (4%; 1-14)	6 (12%; 5-24)
IL-6(-174GG)/TNFa(-308AG)	2 (4%; 1-14)	2 (4%; 1-14)
IL-6(-174GG)/TNFa(-308AA)	1 (2%; 0-11)	1 (2%; 0-11)

By the third trimester the largest proportion of women in the case group had clinical manifestations of genital infection (88%; $\chi^2=11,1$, $p=0,0008$). In patients with genital infection before delivery in every third case placenta was infected - 24 out of 75 (32%; 22-44) to 2 (8%; 1-26) without infection before delivery ($\chi^2=5,6$, $p=0,02$).

The probability of preterm birth in genital infection (table 2) and intrauterine infection (IUI) is analyzed in women with the genotypes IL-6(-174GC)/TNFa(-308GG), IL-6(-174GG)/TNFa(-308GG) and IL-6(-174CC)/TNFa(-308GG).

Table 2 - The proability of preterm birth in patients with the genotypes IL-6(-174GC)/TNFa(-308GG), IL-6(-174GG)/TNFa(-308GG) and IL-6(-174CC)/TNFa(-308GG) in the presence of genital infection, n, p%, 95%CI_p

Genotype	Preterm labor		OR, 95%CI, p
	genital infection	no infection	
IL-6(-174GG)/TNFa(-308GG) N=21	9 (43%; 22-66)	1 (5%; 0-24)	OR=15,0, 95%CI 1,7-133,6, p=0,01
IL-6(-174GC)/TNFa(-308GG) N=53	24 (45%; 32-60)	2 (4%; 1-13)	OR=21,1, 95%CI 4,7-95,8, p<0,0001
IL-6(-174CC)/TNFa(-308GG) N=12	8 (67%; 35-90)	1 (8%; 0-39)	OR=22,0, 95%CI 2,1-236,1, p=0,01

With IUI, the probability of preterm delivery is higher in patients with the IL-6(-174GG)/TNFa(-308GG) genotype - 8 (89%; N=9) to 2 (17%; N=12) women with this genotype and no IUI (OR=40,0, 95%CI 3,1- 524,9, p=0,005).

Conclusions. With genital infection the chance of preterm delivery is increased in patients with the genotype IL-6(-174CC)/TNFa (-308GG), IL-6(-174GC)/TNFa(-308GG) and IL-6(-174GG)/TNFa(-308GG). With genotype IL-6(-174GG)/TNFa(-308GG) and the realization of intrauterine infection, the chances of premature birth are 40 times higher.

Allelic polymorphism of the promoter regions in the human IL-6 and TNFa genes reflects the functional state of the immune system and can be used for timely diagnosis and prevention of preterm labor in patients with genital infection.

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PROLIFERATIVE-APOPTOTIC PROCESSES IN TESTICULAR SEMINOMA

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Testicular tumors, though being equal up to 1% out of all the male neoplasms all over the world, are the most frequent among white men within the period from puberty up to the age of 40 in industrially advanced countries [1]. At that, testicular germ cell tumors (TGCT) amount to more than 90% of all the testicular tumors and seminoma amounts about 50% of them [2]. Objectives: to study the proliferative-apoptotic processes in testicular seminoma.

Materials and Methods. Material was collected in Pathological Anatomy Department of Kharkiv Regional Clinical Centre of Urology and Nephrology named after Shapoval V.I. We analyzed 13 cases of testicular seminoma which were obtained with orchifuniculectomy. Immunohistochemical (IHC) examination was performed by indirect immunoperoxidase reaction. For estimation of proliferative-apoptotic processes the following primary antibodies were used: Mo a-Hu Ki-67 (Monoclonal Antibody, clone MIB-1, «DAKO», Denmark), Rb a-Hu Bax (Polyclonal Antibody, «Thermo Fisher Scientific Inc.», USA), Mo a-Hu Bcl-2 (Monoclonal Antibody, clone100/D5, «Thermo Fisher Scientific Inc.», USA) and Mo a-Hu p53 (Monoclonal Antibody, clone DO-7, «DAKO», Denmark). The reaction was visualized using Ultra Vision Quanto Detection Systems HRP Polymer («Thermo Fisher Scientific Inc.», USA).