Effect of HLA-Compatibility in Married Couples on the Development and Severity of Gestosis

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We studied the effect of histocompatibility in married couples on the development and severity of gestosis. It was found that gestosis more often develops in women with two common HLA alleles of class II major histocompatibility complex with her husband. The greatest number of coincidences was detected in subgroups with medium and severe gestosis. Perinatal outcomes in women with medium-severe gestosis having HLA-alleles common with husbands are characterized by delivery of babies with lower body weight.

Key Words: *gestosis; HLA; compatibility of parents*

Gestosis remains one of the main causes of pregnancy complications (7-19%) and plays the main role in maternal and perinatal morbidity and mortality.

Numerous experimental and clinical studies demonstrated exceptionally important role of immune disorders in the pathogenesis of gestosis [2,4, 6,9,12].

The main event in the pathogenesis of gestosis is initial impairment of the placentation process. Inhibition of the trophoblast invasion in the absence of spiral uterine arteries remodeling (*i.e.* without transformation of their muscular layer) leads to placental hypoperfusion. Placental ischemia is paralleled by the involvement of the endothelium, later acquiring a generalized pattern [2,8].

From immunological viewpoint, the fetus is a semiallogenic transplant, because the genetic fund of the fertilized oocyte is by 50% taken from father. Transplantation of genetically foreign tissue inevitably leads to transplant death or rejection. This does not happen in normal pregnancy due to triggering of immunoprotective mechanisms and formation of anatomic and functional placental barriers [1,2,4].

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Recognition of alloantigens as foreign molecules is determined by the presence of products of highly polymorphic genes of the major histocompatibility complex (HLA in humans). By the present time the role of HLA genes in the functioning of congenital and acquired immunity systems is proven [1].

The role of HLA compatibility in married couples to the genesis of reproductive disorders is now discussed. The degree of histocompatibility seems to be essential for the recognition of paternal HLA determinants inherited by the fetus, by maternal lymphocytes, which, in turn, leads to deficiency of cellular and humoral immunity in the mother—fetus system [6].

Experimental and clinical data on the effect of HLA identity of parents on the development of gestosis are contradictory [6,11].

We analyzed the impact of histocompatibility of parents on the development and severity of gestosis.

MATERIALS AND METHODS

Pregnancy course was studied in 37 couples. The main group consisted of 27 couples in which the present or previous pregnancy was associated with gestosis (including those with perinatal losses). Con-

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trol group consisted of 10 couples with normal gestation.

In addition to common clinical and obstetrical studies, HLA typing of DR, DQA, and DQB locuses was carried out in all pregnant women.

HLA typing of blood samples was carried out at Laboratory of Clinical Immunology of Center of Obstetrics, Gynecology, and Perinatology by the PCR method using commercial kits (DNK-Tekhnologiya) and DNA fluorometer (Hoefer). At the first stage, DNA was isolated from the peripheral blood lymphocytes by modified Higuchi method. The DNA samples were directly used for typing or stored at -20°C. The mean DNA concentration determined by fluorescence with Hoechst 33258 on a DNA fluorometer was 50-100 μg/ml. Total duration of DNA isolation procedure was 30-40 min. PCR was carried out in 10 μl reaction mixture containing 1 μl DNA. The concentrations of primers were selected individually for each mixture. Amplification was carried out on an MC2 multichannel thermocycler (DNK-Tekhnologiya). Identification of amplification products and evaluation of their lengths distribution were carried out in UV light after 15-min electrophoresis.

The results were analyzed and the data were statistically processed using standard statistical software.

RESULTS

The results indicate that gestosis more often develops in women having more than two HLA alleles common with baby's father. Coincidences were detected in 100% couples of the main group and in only 44.4% couples of the control group. One coincidence in HLA genotypes was detected in 18.5% couples of the main group and in 22% of control group couples. Two coincidences of HLA alleles were detected in 33.3% couples in the main group and in 22% in the control group. Coincidences of three alleles were detected in 44% examined couples with gestosis and none in the reference group ($p<0.05$). Four coincidences in HLA genotypes were detected in one couple (3.7%) of the main group.

The number of coincidences was maximum in subgroups with medium-severe and severe gestosis. The identity by three HLA alleles was detected in 54 and 40% couples, respectively ($p<0.05$). Analysis of HLA genotypes of the couples showed identity by HLA-DR locus in 63% of cases with gestoses *vs.* only 11% in the control group.

Coincidences by DQA1 and DQB1 locuses in gestosis were detected in 77 and 66.6% cases, respectively, *vs.* 22% cases in the control group.

The relative risk for pregnant women with gestosis was 5.7 for couples with compatibility by HLA-DR locus alleles, in case of compatibility by DQA1 and DQB1 alleles this index was 3.5 and 3, respectively.

The course of pregnancy was complicated by fetoplacental insufficiency in 11 (40.7%) women in the main group; 13 (48%) children were born with 1st-3rd degree hypotrophy. The mean body weight of all babies born by mothers with gestosis having HLA alleles common with their husbands was lower in comparison with babies whose parents had no identical HLA alleles ($p<0.05$).

Impaired placental perfusion is the main cause of delivery of babies with low body weight. Changes in the immune homeostasis system under conditions of HLA compatibility in married couples lead to disorders in maternal selective tolerance intrinsic of normal gestation, with triggering of the mechanisms of fetus rejection by its antigenic structures by the T_1-helper type. The key role of T_1-helper type response in initiation of spontaneous abortion during early period is known. Analogy with this regularity by similarity of immunological mechanisms suggests regarding gestosis as a clinical form of fetus rejection during the second half of pregnancy, associated with a specific symptom complex [4,7,10].

Our results are in line with published data according to which HLA compatibility of parents by several HLA locuses 4.5-fold increases the risk of gestosis [6].

Our results suggest that coincidence of parents by more than two HLA-II locuses reduces maternal immune system reactivity, resulting in failure of adequate immunological reaction during pregnan-

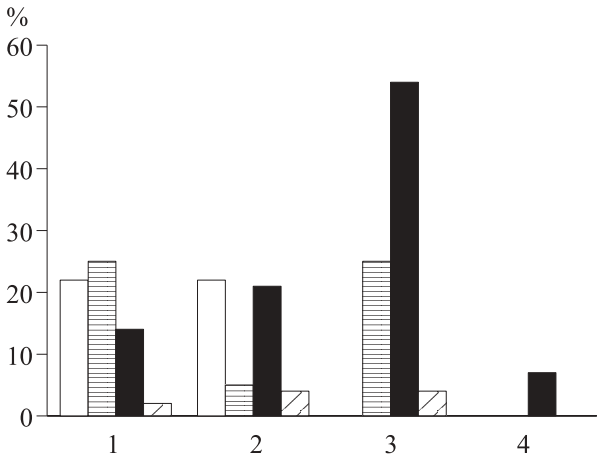

Fig. 1. Number of HLA coincidences (1-4) of parents in examined groups. Light bars: control group; horizontal hatching: mild gestosis; dark bars: medium-severity gestosis; cross-hatching: severe gestosis.

cy. Analysis of immunogenetic determinants of gestosis with consideration for such risk factors as HLA identity of parents significantly extends our notions of the immunological component in the etiology and pathogenesis of this condition.

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