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Changes in the levels of natural autoantibodies during complications of gestation

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Abstract

Natural regulatory autoantibodies (immunoglobulin G) are tools of the immune system to control antigen–molecule homeostasis in an organism. Taking into account the transplacental transfer of immunoglobulin G, the determination and analysis of autoantibody levels during pregnancy will promote the understanding of immunopathological processes underlying normal and impaired gestation. Autoantibodies are becoming more relevant due to the paradigm shift in modern medicine from treatment to disease prevention. This review analyzes scientific research in which the levels of various natural autoantibodies were studied to predict obstetric complications, such as massive bleeding, fetoplacental insufficiency, preeclampsia, delayed fetal growth, and miscarriage. Studies that investigated fetal and perinatal pathologies based on the woman's serum levels ofsome regulatory autoantibodies were of particular interest. The autoantibodies to total myelin protein, S-100 protein (soluble at 100% saturation; calcium-dependent regulator of cellular functions), membrane protein (MP)-65, double-stranded deoxyribonucleic acid, β_2-glycoprotein, cardiolipin, low-density lipoproteins, total phospholipids, chorionic gonadotropin, phosphatidylserine, prothrombin, angiotensin II, platelet membrane antigens, kidney and liver mitochondria, nervous tissue component NF-200 (axonal specific protein), GFAP (astrocyte filament protein), and neuron-specific enolase were most important for pregnancy. A systematic analysis of the dependence of normal gestational course on the serum levels of certain regulatory antibodies will facilitate the identification of new methods for the early detection and prevention of disorders of pregnancy and pathologies in the fetus during pregnancy.

Keywords: pregnancy, regulatory autoantibodies, obstetric complications.

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Pregnancy is a process that affects the entire immune system [1]. In recent years, it has been experimentally proven that a normal course of pregnancy depends on the activity of the placental natural killer cells [2, 3]; ratio of Thl/Th2 lymphocytes [4]; and level of synthesis of many lymphokines [5], cytokines [6], interleukins, and chemokines [7].

Since 15 years, studies have been conducted on the immunopathology during pregnancy using panels of various natural regulatory autoantibodies (a-ABs), such as immunoglobulin (Ig) G [8]. The results of these studies have enabled us to identify the causes and predict severe obstetric pathologies, such as preeclampsia, bleeding, intrauterine fetal hypoxia, and accelerated labor.

Natural regulatory a-ABs are one of the basic molecular tools by which the immune system controls the antigen–molecular homeostasis of an organism and regulates its functions [9]. The range of a-ABs in healthy people of different ages is very similar, their sets being formed during the intrauterine period, with minor differences reflecting immunometabolic individuality [10].

The development of various diseases is due to a persistent disruption in the synthesis and/or disintegration of molecular components of certain cells in our body and is accompanied by the activation of cell apoptosis in certain organs. These disorders, which start long before the clinical manifestation of the disease, are reflected in secondary changes in the production of natural a-ABs specific to each form of pathology [11, 12].

Natural antibodies, which are biologically active regulatory molecules, are needed in strictly determined quantities. An abnormal increase or decrease in the serum levels of many a-ABs can lead to somatic problems that underlie the pathologies of pregnancy, including recurrent miscarriage, missed miscarriage, preeclampsia, and malformations of the fetus [13].

Until recently, a subclass of biologically active a-ABs directly related to the regulation of embryogenesis was studied individually, including a-ABs to the main myelin protein, S-100 protein (soluble at 100% saturation), and fractions of acidic chromatin binding protein (ACBP)-C and membrane protein (MP)-65, which are

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assumed to be embryotropic antibodies. Notably, only IgG antibodies are considered embryotropic because IgM, IgA, or other antibodies cannot penetrate the placental barrier [14].

Accumulating data regarding changes in a-AB levels in various obstetric pathologies has enabled the classification of most regulatory a-ABs synthesized in the body of a pregnant woman as embryotropic, because they transplacentally enter the fetus through active receptor-mediated energy-dependent transport and influence the course of the pregnancy and condition of the fetus. In 1997, Talwar established the fact that a woman's reproductive health is dependent on the level of antibodies to luteinizing hormone, follicle stimulating hormone, and prolactin [15]. According to Cunha and Zancopé-Oliveira (2002), elevated titers of antibodies to nucleic acids had pathological consequences on the course of pregnancy [16].

During the late twentieth and early twenty first centuries, continuous studies were conducted regarding new antigens, where an excess of antibodies could adversely affect the progress of pregnancy. These antigens included pregnancy-specific glycoproteins, maternal antigen that embryos require (MATER) protein [18], cardiac antigens La and Ro (excessive levels of maternal antibodies to these antigens almost inevitably caused persistent disturbances of myocardial functions in the fetus) [19], and renal antigens (excessive levels of maternal antibodies to these antigens caused renal pathologies in the fetus) [20]. Currently, the role of excessive or insufficient production of a-ABs to phospholipids and β_2-glycoproteins, which are one of the criteria for antiphospholipid syndrome, [21-26] in the occurrence of various gestational complications is the most studied. In women with miscarriage, the dynamic evaluation of the degree of increase or decrease in the levels of embryotropic a-ABs to ACBP-14/18 and MP-65 is recommended as a method of monitoring the efficacy of therapeutic measures aimed at suppressing infectious and inflammatory processes, normalizing the hormonal status, and/or correcting pathological autoimmune processes [27].

Effective elimination of the main etiological factors is accompanied by the normalization of the synthesis of embryotropic antibodies and 5–8-fold reduction in the frequency of adverse pregnancy outcomes. In addition, an increased level of antibodies to adenosine deaminase was identified during miscarriage. Adenosine deaminase is a key enzyme in purine metabolism, whose activity is closely associated with immunopathological processes in the body [28].

Studies on a-ABs to S-100 protein, deoxyribonucleic acid (DNA), β_2-glycoprotein, and Ig Fc-fragments in women with a burdened obstetric history (intrauterine fetal death, habitual miscarriage, or preterm delivery) detected that immunoregulatory disorders were detected in the form of decreased levels of embryotropic a-ABs in 16.8% of patients, increased levels in 56.1%, and imbalance in 19.7%; only 7.4% of the women showed no immunoregulatory abnormalities.

According to Nyukhnin, pregnancy in women with a reduced level of antibodies is characterized by the threat of miscarriage, preeclampsia, and delayed fetal growth. An increase in antibody levels is associated with spontaneous abortion and chronic placental insufficiency. Imbalance of a-ABs is accompanied by recurrent miscarriage, undeveloped pregnancy, and preeclampsia [29].

Antibodies can affect all functional and structural components of hemostasis, such as vascular, platelet, coagulation, anticoagulation, and fibrinolytic systems [30, 31]. Disseminated intravascular coagulation syndrome developed in 63% of pregnant women with decreased antibody levels, 59% in those with increased antibody levels, and 91% in those with antibody imbalance. The most severe changes in the hemostasis system were observed in women with imbalanced and pathologically lowered antibody levels [29].

According to Radzinsky et al., the degree of severity of placental insufficiency can be determined by the levels of a-ABs to main myelin protein, S-100 protein, ACBP-C, and MP-65. Placental insufficiency occurred in 33.3% of cases with a moderate a-AB level deviation toward hyporeactivity, 42.1% of those with a moderate a-AB level deviation toward hyperreactivity, 76.3% of those with a pronounced a-AB level deviation toward hyporeactivity, and 85.7% of those with a pronounced a-AB deviation toward hyperreactivity [32].

The role of natural a-ABs in the development of preeclampsia [33] and gestational arterial hypertension [34] is being actively studied. The association between the occurrence of preeclampsia and levels of a-ABs to cardiolipin, low-density lipoproteins, β_2-glycoprotein [35], angiotensin [36], DNA [25], phosphatidylserine, prothrombin [37], angiotensin II [38], nucleic acids, phospholipids [39], glial fibrillary acidic protein (GFAP), and neuron-specific enolase [40] has been studied.

In 64% of pregnant women with moderate or severe preeclampsia, an imbalance in regulatory a-AB levels was identified 10–16 weeks before the appearance of first clinical symptoms of preeclampsia. This included a decrease in the levels of a-ABs to MP-65, nitroxide synthetase, antineutrophil cytoplasmic antibodies (vasculopathy marker), NF-200, and GFAP; increase in the levels of a-ABs to DNA, total phospholipids, and β_2-glycoprotein; and decrease in all a-AB levels in 30% of women [41].

According to Makarov, Bogatyryov, and Osipova, the determination of the serum levels of a-ABs of the IgG class to double-stranded DNA, platelet membranes antigens (TrM-001-15, TrM-015-120), renal antigens (KiM-05-300, KiS-07-120), and liver mitochondrial antigens (HMMP) optimizes the differential diagnosis of preeclampsia and chronic hypertensive conditions in women at 24–35 weeks of gestation. It also enables to predict the development and severity of preeclampsia at 2–4 weeks before the appearance of the first clinical symptoms, improves perinatal outcomes, and reduces maternal and infant morbidity and mortality [42].

The changes in the levels of natural a-ABs in pregnant women in the third trimester, characterized by a marked decrease in the levels of a-ABs to platelet proteins (TrM) and significant increase in the levels of a-ABs to total phospholipids, preceded excessive bleeding in labor in 87% of patients, whereas an isolated increase in the levels of a-ABs to platelet proteins was recorded in pregnant women with moderate blood loss [43].

Among women who underwent in vitro fertilization for ≥2 times, a persistent increase in the levels of a-ABs to human chorionic gonadotropin occurred 10 times more often than that in the general population of pregnant women (2%), and was characterized by higher specific immunoreactivity values [44].

Studies that predicted the condition of the fetus by taking into account the serum levels of a-ABs in pregnant women were of particular interest. Increased serum levels of a-ABs to the main myelin protein, S-100 protein, fractions of anionic nonhistone chromatin proteins, and membrane protein of the brain in pregnant women was a prognostic criterion for the onset of intrauterine hypoxia of the fetus; a reduced level of these a-ABs was associated with increased newborn morbidity rates [45].

Tareeva et al. used a-AB levels to the main protein of myelin and S-100 protein to predict perinatal pathology. They claimed that implementing adequate therapeutic and prophylactic measures for pregnant women with deviations in the levels of the abovementioned a-ABs resulted in a reduction in the incidence of severe intrauterine infections from 26% to 11%, and in the frequency of perinatal pathology from 25% to 13% [46].

According to Klyuchnikov, an integral assessment of the health of children under observation from the neonatal period until 4 years of age indicated that 80% of women with normal embryotropic a-AB levels gave birth to healthy children. By the age of 4 years, 75% of these children remained healthy. On the contrary, the more pronounced the deviation in the embryotropic a-AB levels in pregnant women, the less likely they were to give birth to healthy children [47].

Thus, studies aimed at identifying regulatory antibodies that pass from a pregnant woman to her fetus and detailed systematic study of the dependence of normal course of gestation on the serum levels of certain types of regulatory antibodies in pregnant women contribute to finding new ways to maximize early detection of risk groups and diagnosis of gestational and fetal pathologies.

The research of a-ABs is becoming more relevant, primarily because of the paradigm shift in modern medicine from treatment to prevention of disease. Currently, studies are being conducted for determining the role of regulatory a-ABs in predicting pregnancy-related pathologies and childbirth.

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