

The effectiveness of complex prevention of preeclampsia using immunoglobulins

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ABSTRACT

The purpose of this study has been to research the effectiveness of complex prevention of preeclampsia using immunoglobulins.

130 pregnant women with various risk factors for preeclampsia who received various methods of preventing preeclampsia during the gestation period have been examined. Pregnancy outcomes, the frequency and structure of hypertensive disorders, the timing and methods of delivery, as well as the rate of morbidity and mortality in newborns depending on the method of preventive therapy of hypertensive disorders have been studied in the compared groups. To assess the relationship between the qualitative characteristics, the Pearson χ^2 criterion has been used. The study has found that traditional prophylaxis reduces the development of hypertensive disorders by almost 2 times ($p < 0.05$), preventive therapy with immunocorrection developed by us has been 4 times more effective ($p < 0.01$) when compared with pregnant women who failed to receive preventive treatment. The proposed method has allowed us to prevent severe forms of pathology and such pregnancy complications as intrauterine growth retardation and antenatal foetal death. The frequency of birth of premature babies has decreased 3.3 times compared with patients without treatment and 3 times when compared with pregnant women who received conventional methods of prevention. The overall incidence of newborns has decreased by 1.5 times in the group with conventional treatment compared with pregnant women without treatment and 3 times in the group who received prophylaxis using the new method.

Keywords : preeclampsia, prophylaxis, immunoglobulins

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I. INTRODUCTION

Hypertensive disorders during pregnancy occupy a leading position among the problems of modern obstetrics, since they significantly affect the indicators of both maternal and perinatal morbidity and mortality. The frequency of hypertensive disorders varies in a wide range, from 5 to 22% [1] [2] [3]. This indicator depends on many factors, primarily on the level of socio-economic development of the country, the ethnicity of the pregnant woman, as well as the quality and availability of medical care, increase in the overall morbidity among women and the number of pregnant women of late reproductive age. Numerous studies show the pathological effect of hypertensive disorders on the condition of foetus [4]-[8]. Despite modern advances in the prevention, diagnosis and treatment of hypertensive disorders during pregnancy, the rate of severe forms ranges from 5 to 10% and has no tendency to decrease [9] [10] [11], and perinatal mortality is 3-4 times higher than the population mortality rate of 18 up to 30% [4]-[8], [12]. Every fourth child with this pathology has the consequences of hypoxia [2],[6]. Perinatal morbidity also does not have a steady downward trend (463.0-780.0 per 1000) [11], [12]. Perinatal morbidity and mortality in preeclampsia is due to prematurity, chronic hypoxia, intrauterine foetal growth retardation [1],[2],[5],[6]. Preeclampsia accounts for up to 15% of the causes in the structure of preterm labour [12]. Since hypertensive

disorders during pregnancy lead to an increase in the frequency of preterm birth, an increase in the number of low-birth and very premature babies is observed respectively. This creates certain difficulties in their care, entails large material costs, in some cases leads to disability, and requires long-term rehabilitation and adaptation of these children to society in the future. Therefore, the problem of hypertensive disorders is not only medical, but also social.

Today there are many (more than 30) different theories explaining the causes of hypertensive states during pregnancy - endothelial, neurogenic, hormonal, immunological, placental, genetic, etc. [13],[14],[15]. However, the final etiology of this pathology is not known. It has been established that the basis for development of preeclampsia is laid as far back as in the early stages of pregnancy.

One of the recognized theories of the development of pregnancy hypertensive disorders is the immunological theory, according to which maternal immune tolerance to paternal placental and foetal antigens is impaired. The risk of preeclampsia increases significantly in conditions where formation of blocking antibodies to placental antigenic areas is disturbed, with the first pregnancy carrying a higher risk. Impaired tolerance explains the increased risk of preeclampsia with a high paternal antigen load - if there are two sets of paternal chromosomes ('double dose') which is typical for women with multiple pregnancy and cystic mole [16]. It has been established that this group of pregnant women have a high incidence of early-onset preeclampsia. Conversely, women previously exposed to paternal antigens, for example, with a previous pregnancy from the same partner, are 'immunized' against preeclampsia. The hypothesis suggests that risk of preeclampsia is increased among women who have limited partner sperm exposure. This hypothesis is supported by the fact that among the multiparous women, women with miscarriages in medical history and the long-term pre-pregnancy period of cohabitation, there is a lower risk of preeclampsia. Conversely, a higher risk of preeclampsia is observed among women who use barrier methods of contraception and those who change sexual partners.

Today, the role of various natural autoantibodies in formation of pregnant hypertension is being actively studied. The relationship between the occurrence of preeclampsia and the level of antibodies to cardiolipin, B-2-glycoprotein-1, angiotensin, DNA, phosphatidylserine, prothrombin, angiotensin-II, S-100 proteins, etc. has been investigated [17],[18],[19],[20],[21]. Publications of recent years testify to the successful use of medicamental immunocorrective agents in treatment of pathological conditions of various etiologies during period of gestation [22],[23], [24], [25], [26].

The **purpose** of this study has been to study the effectiveness of complex prevention of preeclampsia using immunoglobulins.

II. MATERIAL AND METHODS

130 pregnant women with risk factors for hypertensive disorders starting from Trimester I of gestation (up to 15 weeks of pregnancy) have been examined. Depending on the preventive measures taken, the examined pregnant women have been divided into three groups:

Group 1 - 50 pregnant women who did not receive medication prophylaxis of possible hypertensive disorders;

Group 2 - 40 pregnant women who received common traditional methods for prevention of hypertensive disorders;

Group 3 - 40 pregnant women who have been given immunocorrective therapy, along with traditional methods of preventing hypertensive disorders.

The criterion for selection of patients has been availability of various clinical, anamnestic and immunological markers of preeclampsia which were assessed in terms of 10-15 weeks of pregnancy. Special attention has been paid to the main risk factors of preeclampsia, such as age (up to 18 years and over 35 years), parity (primigravidae or re-pregnant), time between births with repeated pregnancies (up to 2 years or more than 10 years), increased body mass index more than 30, baseline systolic and diastolic pressure, premorbid background (diseases of the cardiovascular system, kidney, endocrinopathy, varicose veins, antiphospholipid syndrome, etc.), past reproductive losses (trophoblastic disease, antenatal foetal death, intrauterine growth retardation, undeveloped pregnancy, etc.), unfavourable family history (hypertension, heart attack, stroke, thrombophilic disorders, diabetes mellitus in next of kin, cases of preeclampsia, eclampsia, infertility in mother, sisters and etc.). The generative function of the examined individuals has been subjected to a detailed analysis (infertility, polycystic ovary, use of assisted reproductive technologies in the treatment of infertility, etc.). The immunological risk factors for preeclampsia were: pathological increase in autoantibody titer to β -glycoprotein, antibodies to S-100 proteins, immunosuppressive state of the general immune reactivity of body, decrease in the level of placental growth factor to 100 pg/ml in the blood of pregnant women at 10-15 weeks of pregnancy. Evaluation of the general characteristics of pregnant women showed the homogeneity of the studied groups which has allowed us to compare the clinical course of pregnancy and the results of use of therapeutic measures in this cohort of women. A preventive complex for treatment of preeclampsia has been prescribed without fail until Week 16 of gestation, since it was proved to be effective precisely at a timely start, before formation of placenta.

To date, the following measures have been proven to be effective in preventing preeclampsia and its complications in women with *low risk*: prescription of calcium supplements (1 g/day orally) to women with low dietary calcium (<600 mg/day), vitamin complexes with folic acid, quitting smoking, alcohol and physical exertion.

For prevention of preeclampsia and its complications in women at *increased risk*, it is recommended to take calcium supplements (1 g/day) in case of its low consumption, as well as aspirin at a low dose (75-162 mg/day) before bedtime, the intake begins after Week 12 of pregnancy (but no later than Week 16) and lasts up to 32 weeks. Prophylactic doses of low molecular heparins may be given to women with placental complications (including those with preeclampsia) in a medical history. Use of L-arginine, taking multivitamins with folic acid, increasing the length of home rest in the third trimester and reducing the load and stress, abstaining from alcohol and smoking is considered useful. These recommendations [27], [28], [29] have formed the basis of therapeutic and prophylactic measures applied in our paper. Based on the fact that the immune system of pregnant women with hypertensive disorders undergoes certain changes, we have attempted to combine use of generally accepted traditional and immunocorrective therapy in the complex prevention of these disorders. In recent years, clinicians have increased interest in methods of influencing the immune system during pregnancy. Publications of recent years testify to the successful use of drugs that have an effect on a particular link of immunity in the treatment of pathological conditions of various etiologies during the period of gestation. In our work, the choice of medicamental immunomodulating agents has been carried out taking into account the rational, physiological and safe effects on the body of a pregnant woman and fetus. Therefore, we have used immunoglobulins as an immunocorrective agent. Their protective function is due to the ability to specifically interact with various antigens. The normal human immunoglobulin is an immunologically active protein fraction isolated from human blood plasma of healthy donors. In recent years, this drug has been widely used in obstetric practice for immunodeficiency states, miscarriage and other pathologies of the gestational process [22]-[26]. Normal human immunoglobulin has been prescribed by us to pregnant women in a dose of 25-50ml intravenously drip on physiological solution, up to 4 injections for 2 weeks (2 times a week) in Trimesters I, II and III of pregnancy. The pregnant women of Group 3 have been subjected to the treatment by the proposed method. In order to assess the effectiveness of treatment and preventive measures, the outcomes of pregnancy, the frequency and structure of hypertensive disorders, the timing and methods of delivery, as well as the rate of morbidity and mortality in newborns depending on the method of preventive therapy of hypertensive disorders have been studied in the compared groups. The data obtained in the study have been processed by statistical methods using Pearson χ^2 criterion.

III. RESULTS AND DISCUSSION

The study of the course of the gestational process in the first half of pregnancy has showed that relatively often there was a beginning miscarriage, early toxicosis, asymptomatic bacteriuria and anaemia in all groups. And, for virtually all complications, no statistically significant differences between the compared groups have been

found. The exception has been infection of pregnant women with an acute viral infection (not observed in any patient of Group 3) and urinary tract infections - in Group 3 this pathology has complicated pregnancy 2.7 times less compared with other groups ($p<0.05$) which may be due to the immunocorrective effect of immunoglobulin. Along with this, in 12% of pregnant women who have not received prevention of preeclampsia, and in 7.5% of pregnant women who have received the traditional preventive complex, gestational hypertension developed from Weeks 24-25 of gestation (1.6 times more often; $p<0.05$), while this complication was absent in patients with immunocorrective therapy. A study of the course of pregnancy in Trimester III has showed that, in general, development of hypertensive disorders has been observed in 35 (70.0%) pregnant women of Group I, in 15 (37.5%) in Group II and in 7 (17.5 %) Group III. These data suggest that traditional prevention has reduced the development of pathology by almost 2 times ($p<0.05$), and the preventive therapy developed by us - by 4 times ($p<0.01$). Moreover, the best results for all complications of Trimester III have been observed in patients of Group 3: there were no such complications as severe preeclampsia, hypoxia, intrauterine growth retardation (IUGR) and antenatal foetal death, HELLP (hemolysis, elevated levels of liver enzymes, thrombocytopenia) syndrome, eclampsia. Gestational hypertension in this group has occurred in 12.5% of pregnant women, which is 2.4 and 1.4 times less compared with Groups 1 and 2, respectively; moderate preeclampsia has been observed 4.4 and 2.5 times less frequently than in Groups 1 and 2. Differences in the studied groups have been also revealed in the incidence of premature placental abruption. Thus, conventional prevention contributes to a slight decrease in the frequency of premature placental abruption (statistically insignificant), while the method of prevention developed by us shows a statistically significant decrease in the incidence of this pathology by 2.4 times. In the group of pregnant women who did not receive prophylaxis of hypertensive states, antenatal foetal death has been observed in 4% of cases, which has not been observed in women of Groups 2 and 3. At the same time, perinatal mortality in Group 1 was 66.7% with gestational hypertension and 300% with preeclampsia, and in Group 2 it was 125% with preeclampsia and was absent in Group 3.

Prior to Week 28 of pregnancy, hypertensive disorders have manifested in almost every third pregnant of Group 1, in every fifth - in Group 2 and have not been observed in pregnant women of Group 3. The onset of hypertensive disorders in terms of 28-34-week gestation has been observed with the same frequency in women of Groups 1 and 2 (40%), and in Group 3 it has been observed 2.8 times less often ($p<0.05$), in 14.3% of pregnant women. More later (after 35-week gestation) onset of hypertensive disorders in Group 3 has been recorded in the overwhelming majority of cases (85.8%), which once again underlines the effectiveness of the preventive measures proposed by us.

In the course of the study, we have analyzed the outcomes of pregnancy and methods of delivery with hypertensive disorders against the background of various

methods of prevention and without it. It has turned out that with implementation of preventive measures, an improvement in the outcomes of pregnancy is noted: the frequency of caesarean section and earlier termination of pregnancy is reduced, and the gestational period of pregnancy increases with delivery. So, in Group 1, abortion up to 28 weeks has been observed in 10% of cases with the development of preeclampsia (not observed in other groups). Premature birth in gestational periods up to 34 weeks has been observed in Group 1 in almost every second pregnant woman, in Group 2 in 26.7% and have not been observed in Group 3; in terms of gestation more than 34 weeks - respectively in 40, 60 and 28.6% of patients. Timely delivery in Group 1 has occurred only in 5.7% of pregnant women with gestational hypertension, in Group 2 - in 13.3% of patients also with gestational hypertension, in Group 3 this figure has been 71.4% which significantly higher than in the first two groups.

Analysis of the delivery method has showed that operative delivery in patients of the three groups was observed in 62.9%, 40% and 14.3% of cases, respectively, i.e. decreases against the background of the proposed preventive therapy by 4.4 times when compared with pregnant women who do not receive drug prevention of preeclampsia and 2.8 times compared with pregnant women who receive traditional preventive treatment. Moreover, the frequency of caesarean section in preeclampsia prevailed over the natural method of delivery only in Group 1 of pregnant women ($p < 0.05$), in Groups 2 and 3 it was the same.

With gestational hypertension, the frequency of operative and natural labour in Group 1 was almost the same, in Group 2 - natural delivery was observed 2.5 times more often, and in Group 3, all pregnant women passed through the birth canal. Thus, statistically significant differences in outcomes of delivery have been obtained only in the group of pregnant women with preeclampsia.

For a more complete assessment of the effectiveness of therapy, we have studied the condition of newborns in the groups of pregnant women examined. As a result of the conducted research, the improvement of a number of indicators in the state of newborns depending on the methods of therapy has been established. Thus, with the traditional treatment of gestational hypertension (Group 2), a statistically significant increase (2.2 times; $p < 0.05$) in the percentage of full-term babies has been observed compared with Group 1. While with the proposed preventive therapy (Group 3), the frequency of birth of full-term newborns was 6 times higher ($p < 0.01$) than in Group 1, which emphasizes the effectiveness of the method developed by us. Similar differences have been obtained when analyzing the overall incidence and mass of infants. With preeclampsia in future mothers, the frequency of birth of premature babies in Groups 1 and 2 has been almost the same, and in Group 3 - 2 times lower ($p < 0.05$). There has been an improvement in other indicators of the state of the newborn: a decrease in the frequency of birth of newborns with intrauterine growth retardation by almost 1.5 times against the background of generally accepted prevention

($p < 0.05$) and the absence of cases of IUGR in Group 3; reducing the overall incidence of newborns.

In this article, we present the clinical case for prevention of preeclampsia using immunoglobulins.

Clinical case.

Re-pregnant, 40 years old, addressed the Outpatient Department of the RIOG for a pregnancy of 6-7 weeks.

From the anamnesis - this pregnancy is the fourth, Pregnancy 1 ended in an abortion at 6-7 weeks of pregnancy 10 years ago, Pregnancy 2 ended in spontaneous miscarriage at 9 weeks 4 years ago, Pregnancy 3 was in a second marriage and ended in emergency operative delivery a year ago, due to the development of eclampsia at Week 32, a girl weighing 1,800 was born. Family history is burdened by maternal hypertension and preeclampsia in the sister during gestation. Somatic history - in childhood, she suffered from viral hepatitis A, rhinoplasty operation was performed 5 years ago due to a curvature of the nasal septum, and is monitored by an endocrinologist for autoimmune thyroiditis.

Objective data: height - 174cm, weight - 68kg, IMT - 22.5. Initial blood pressure - 110/70 mm Hg. Considering the burdened obstetric and family history of hypertension, at Week 12 of pregnancy, the level of placental growth factor in the blood of the pregnant woman and the immunological markers of preeclampsia - antibodies to S100 proteins, HCG, DNA, B2-glycoprotein were determined. As can be seen from the data in Fig., the immunological reactivity of the organism of this patient was in a state of immunosuppression, from the immunological markers a pathological increase in AB to S100 and AB to B2-glycoprotein was established. Studying the level of PGF in the blood of the pregnant woman showed a significant decrease (49pg/ml), which also allowed this patient to be at an increased risk of developing preeclampsia with IUGR of the fetus (Fig. 1). Thus, the pregnant woman, along with clinical and anamnestic risk factors, also had immunological markers of preeclampsia.

Based on the data obtained, the pregnant woman was offered a course of prevention of preeclampsia with immunocorrective therapy. From Week 13 of pregnancy up to Weeks 32-34, the patient received aspirin at a dose of 100 mg/day, calcium preparation -1.0 g/day, a prophylactic dose of NMH (fraxiparin 0.3 p/c), as well as immunoglobulin infusion IV 50ml 2 times a week 4 infusions at Weeks 14-16, 24-26 and 32-34 of gestation. The patient was also prescribed multivitamin preparations with a high content of folic acid throughout pregnancy.

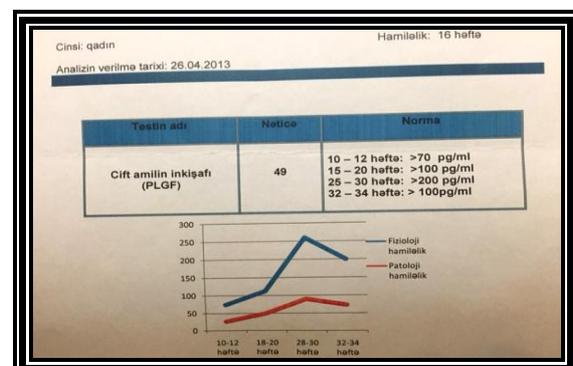


Fig. 1. The level of placental growth actor (15-16 weeks).

In the second trimester, a dopplerometric study of the placental complex was performed which revealed normal parameters of the uteroplacental and fetoplacental blood flow in the uterine arteries and umbilical arteries (see Fig. 2,3).

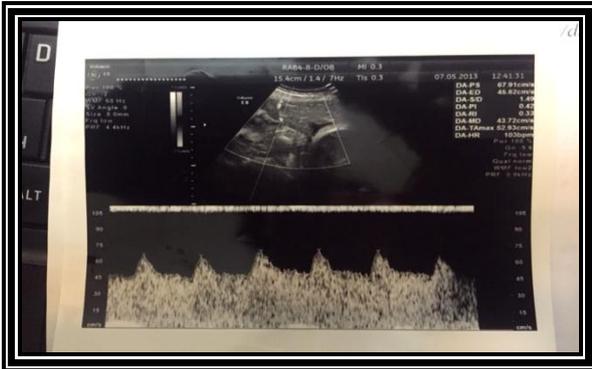


Fig. 2. Dopplerometry. Blood flow in the right uterine artery (IR-0.33).

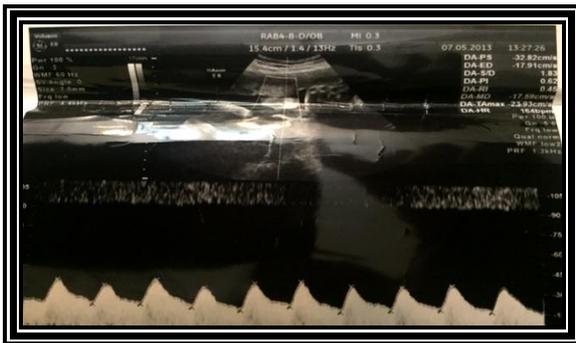


Fig. 3. Dopplerometry. Blood flow in the umbilical artery.

The course of pregnancy - in the second trimester, pregnancy was complicated by the development of hypothyroidism which required hormonal correction, as well as mild anaemia. At Week 36-37 of pregnancy, moderate gestational hypertension was added which does not require medical correction. Indicators of non-stress test on KTG in the dynamics did not reveal signs of suffering of the foetus and at Weeks 38-39 of pregnancy, the patient routinely underwent surgery, a girl was born weighing 3.500g, height 51cm, Apgar score 8/8 points.

Thus, the analysis of this case showed that with both clinical-anamnestic and immunological risk factors for preeclampsia, timely comprehensive preventive therapy with immunocorrection helps prevent severe forms of preeclampsia and leads to favourable outcomes for mother and foetus.

IV. CONCLUSION

The study has found that conventional prevention reduces the incidence of hypertensive disorders during pregnancy by almost 2 times ($p < 0.05$), while the preventive therapy developed by us was 4 times more effective ($p < 0.01$) when compared with pregnant women who have not received preventive treatment.

The proposed prevention of hypertensive disorders using immunocorrection has prevented severe forms of pathology and such complications as IUGR and

antenatal foetal death, significantly reduced the incidence of premature and operative labour, rates of perinatal mortality and overall morbidity in newborns, etc. Treatment and preventive measures from the end of Trimester I of gestation throughout the gestational period, which contributes to a significant improvement in pregnancy outcomes for both mother and foetus are recommended to pregnant women with various risk factors of preeclampsia.

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