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(RESEARCH ARTICLE)

The role of immunotherapy in prevention of preeclampsia and influence on the condition of pregnant women and newborns

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Abstract

Despite on modern success in the prevention, diagnosis, and treatment of hypertensive disorders (HD) in pregnancy, the preeclampsia (PE) affects around 2 to 5% of pregnancies, and has no tendency to decrease, and perinatal mortality is from 18 to 30%. The aim of the provided study was to investigate the condition of the pregnant women and newborns born from mothers with various HD depending on the method of prevention of this pathology. It was analyzed the condition of 130 pregnant women and newborns from mothers at risk for PE, which received various methods of PE prevention during pregnancy. In groups studied pregnancy outcomes, frequency, and the structure of HD, methods of delivery, the incidence of morbidity, and mortality of newborns depending on the method of preventive therapy of HD. The Pearson criterion χ^2 was used to assess the relation between quality signs. During of the study it was established that traditional preventive treatment reduces the development of hypertensive disorders almost by 2 times ($p < 0.05$), the preventive therapy with immunotherapy developed by us proved to be effective by 4 times ($p < 0.01$) in compare with pregnant women who did not receive preventive treatment. The prevention of HD during pregnancy with using immunotherapy allowed preventing severe forms of pathology and complications, such as intrauterine growth restriction and antenatal fetal death, significantly reduced frequency of premature and operative births, indicators of perinatal mortality and general morbidity of newborns.

Keywords: Preeclampsia; High-Risk Pregnancy; Prevention; Newborn; Immunotherapy**.**

1. Introduction

Despite on modern success in the prevention, diagnosis, and treatment of hypertensive disorders (HD) in pregnancy, the preeclampsia (PE) affects around 2 to 5% of pregnancies [1-7], and perinatal mortality is 3-4 times higher than in the population and is 18 to 30% [8]. Perinatal morbidity is 463.0-780.0 per 1000 [9]. Perinatal morbidity and mortality rate at PE depends on degree of prematurity, placental insufficiency, intrauterine growth restriction (IUGR) [10, 11]. The rate of PE in the structure of preterm births is around 15% of the causes [12]. One of the most unfavorable complications in PE remains placental insufficiency, which leads to IUGR [13].

Since HD in pregnancy lead to increasing in the frequency of premature births, a rising is observed in the number of low birth weight (LBW) infants and extremely premature infants accordingly. And this could be causes of certain difficulties in their care, entails high material costs, leads to disability in some cases, and requires long-term recovery and adaptation of such children to society in the future [10, 11].

Immunological regulation by which pregnancy is maintained is a central problem in the field of reproductive immunology. There are some works concerning immunotherapy for recurrent miscarriage [14, 15]. Also, immunological changes could influence on the pregnancy in women with high risk for PE and provide the manifestation of complications [16, 17, 18].

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The aim of the provided study was to investigate the condition of the pregnant women and newborns born from mothers with various HD depending on the method of prevention of this pathology.

2. Material and methods

The 130 pregnant women at risk for PE were examined starting from the first trimester of gestation (before 12 weeks of pregnancy) based on the preventive measures was divided into three groups:

Group 1 - 50 pregnant women did not receive prevention therapy of possible HD;
Group 2 - 40 pregnant women received generally accepted traditional methods for the prevention of HD;
Group 3 - 40 pregnant women received immunotherapy along with the traditional methods for the prevention of PE.

It had be taken necessary appropriate approval for providing the study and also a written consent from patients involved in the study ensuring their acceptance in the study and publication of relevant data in the journal. So, informed consent was obtained from all individual participants included in the study.

Women identified as high-risk were scheduled for more intensive antenatal surveillance and prophylactic interventions. Current strategies for risk assessment were based on the obstetric and medical history and clinical examination. The measure for the selection of patients was the presence of various clinical, anamnestic, and immunological markers of PE. It was given attention to the main risk factors for PE, such as age (up to 18 and above 35 years), parity (prime or multiparous), the time interval between births in repeated pregnancies (up to 2 years or over 10 years), increased body mass index (BMI) over 30, similar indicators of systolic and diastolic blood pressure, previous history (diseases of the cardiovascular system, kidneys, endocrine pathology, varicose veins, antiphospholipid syndrome (Lupus), etc.), reproductive losses in the past (the presence of trophoblastic disease, antenatal fetal death, IUGR, missed miscarriage, etc.), burdened family history (the presence of hypertension, heart attack, stroke, thrombophilia disorders, diabetes in close relatives, cases of PE, eclampsia, infertility in mothers, sisters, etc.). The reproductive function of the woman (infertility, polycystic ovary, assisted reproductive technologies in the treatment of infertility, etc.) is needed to a detailed analysis. The following markers established by us in previous studies were classified as immunological risk factors for PE: pathological increase in the level of autoimmune antibodies (Antineutrophil Cytoplasmic Antibodies (ANCA), antibodies to B-glycoprotein, antibodies to S-100 proteins) and the immunosuppressive state of the body's overall immunological reactivity and a reduction in the level of placental growth factor to 100 pg / ml in the blood of pregnant women in the 10-15 weeks of pregnancy [19]. Evaluation of the general features of pregnant women showed the homogeneity of the studied subgroups, which allowed us to compare the clinical course of pregnancy and the results of the application of therapeutic interventions in this group of women.

To date, the effectiveness of the applied prevention for PE and its complications in women at low-risk for PE has been proven: prescribing of calcium preparation (1 gr /day per os) to women with a low calcium content in the diet (<600 mg/day), multivitamins with folic acid, stop smoking, alcohol and physical effort.

With the aim to prevent PE and its complications in women at increased risk, it is recommended to prescribe calcium preparation (1 gr/day) in case of its low consumption, as well as Aspirin in a low dose (75-162 mg/day) before bedtime, administration begins after 12 weeks pregnancy, but up to 16 weeks and lasts up to 32 weeks. Prophylaxes doses of low-molecular-weight heparins prescribed to women with placental complications (including preeclampsia) in history. It is considered useful to use L-arginine, take multivitamins with folic acid, increase the duration of home rest in the third trimester, and to reduce load and stress, the abstinence from alcohol and smoking. These recommendations formed the basis of the treatment and preventive measures applied in our work.

Based on the fact that the immune system of pregnant women with HD undergoes certain changes, we attempted the combined use of generally accepted traditional and immunotherapy in the comprehensive prevention of these disorders. In recent years, clinicians have increased interest in methods of influencing to the immune system in pregnancy. Publications of recent years indicate the successful use in the treatment of pathological conditions of various causes in the gestation period of drugs that affect one or another part of immunity [15-17]. In our work, the choice of medication with immunomodulatory agents was carried out considering the rational, physiological, and safety impact on the body of a pregnant woman and fetus. Therefore, as an immunotherapy agent, we implemented immunoglobulins. Their protective function is due to the ability to specifically interact with various antigens. The preparation "normal human immunoglobulin" is an immunologically active protein fraction, isolated from the human blood plasma of healthy donors, and individually tested for the antibodies to human immunodeficiency virus (HIV), hepatitis C virus, and absence of surface antigen of hepatitis B (HBsAg) virus. In recent years, this drug has been widely used in obstetric practice for immunodeficiency states, miscarriage, and other pathologies of the gestational process [13,14].

A normal human immunoglobulin was prescribed by us to pregnant women at a dose of 25-50 ml intravenously in saline, up to 4 infusions during two weeks (2 times a week) in the first, second, and third trimesters of pregnancy. Pregnant women in the 3rd group were treated with the proposed method.

To evaluate the effectiveness of treatment and prophylactic measures in the compared groups, the outcomes of pregnancy, the frequency, and structure of HD, the timing and methods of delivery, as well as the morbidity and mortality rate of newborns, depending on the method of preventive treatment of hypertensive disorders, were studied. The data obtained during the study were processed by statistical methods. The Pearson criterion χ^2 was used to assess the relationship between quality signs.

3. Results and discussion

A study of the gestational course in the first half of pregnancy showed that relatively often, in all groups there were a miscarriage, early toxicities, asymptomatic bacteriuria, and anemia. Moreover, no statistically significant differences were detected between the compared groups for almost all complications. The exception was infection of pregnant women with acute viral infection (not observed in any patients of group 3) and urinary tract infection - in group 3 this pathology complicated the course of pregnancy by 2.7 times less often than in other groups ($p < 0.05$), which is possibly due to immunotherapy influence of immunoglobulin. Besides, 12% of pregnant women who did not receive prevention for PE and 7.5% of pregnant women who received a traditional prophylaxis complex have developed gestational hypertension in 24-25 weeks of pregnancy (1.6 times more often, $p < 0.05$), while patients with immunotherapy did not have this complication. The study of the pregnancy in its second half of pregnancy showed in Table 1 that, in general, the development of HD was observed in 35 (70.0%) pregnant of group 1, in 15 (37.5%) of group 2 and in 7 (17.5%) of group 3.

Table 1 The frequency of complications in the third trimester of pregnancy in pregnant women with various methods of preventing HD.

Complications	**Groups examined**			**P**
	I group (n=50) Total %	II group (n=40) Total %	III group (n = 40) Total %	
Gestational hypertension	15 30,0	7 17,5	5 12,5	1-2<0,05 1-3<0,05 2-3>0,05
Moderate Preeclampsia	11 22,0	5 12,5	2 5,0	1-2<0,05 1-3<0,01 2-3<0,05
Severe Preeclampsia	9 18,0	3 7,5	-	1-2<0,05
IUGR	7 14,0	2 5,0	-	1-2<0,05
HELLP syndrome	1 2,0	-	-	-
Eclampsia	1 2,0	-	-	-
Placental abruption	6 12,0	4 10,0	2 5,0	1-2>0,05 1-3<0,05 2-3<0,05
Antenatal fetal death	2 4,0	-	-	-
Perinatal mortality	7 140,0‰	2 50‰	-	1-2<0,05

These data shows that traditional prevention reduced the development of pathology by almost 2 times ($p < 0.05$), and the preventive therapy with immunotherapy was effective by 4 times ($p < 0.01$). Moreover, the best results for all complications prevention in the third trimester were observed in the patients of Group 3: there were no such complications as severe PE, IUGR, antenatal fetal death, HELLP syndrome, and eclampsia. Gestational hypertension in this group occurred in 12.5% of pregnant women, which is 2.4 times and 1.4 times less compared with Group 1 and Group 2, respectively; moderate PE was observed 4.4 times and 2.5 times less frequently than in Group 1 and 2.

Differences in the studied groups were also revealed by the frequency of development of premature placental abruption (PPA). Thus, conventional prevention contributes slight reduction in the frequency of PPA, which has no statistical significance, while with the prevention method developed by us, a statistically significant decrease is observed by 2.4 times in this pathology. In the group of pregnant women who did not receive prevention of HD, antenatal fetal death was observed in 4% of cases, which we did not observe in women of Group 2 and 3. Furthermore, perinatal mortality in Group 1 was 66.7 ‰ for gestational hypertension and 300 ‰ for PE and in Group 2 was 125‰ for PE, and there was no in Group 3.

Until the 28 weeks of pregnancy, HD were manifested in each third pregnant in group 1, in each fifth - in Group 2, and were not observed in pregnant Group 3. The onset of HD in the gestation of 28-34 weeks was observed with the same frequency in women of Group 1 and 2 (40%), and was observed 2.8 times less frequently ($p < 0.05$) in 14.3% pregnant women in Group 3. Later (after 35 weeks), the onset of HD in Group 3 was recorded in the vast majority of cases (85.8%), which once again emphasizes the effectiveness of the preventive measures proposed by us.

During the study, we analyzed the outcomes of pregnancy and delivery methods (normal birth or C-section) in HD in the presence and absence of various methods of prevention. It was observed that during the implementation of preventive measures, an improvement in pregnancy outcomes is noticed: the frequency of C-section and earlier termination of pregnancy is reduced, the gestational age of pregnancy in delivery is increased, accordingly. So, in Group 1, termination of pregnancy until 28 weeks was observed in 10% of cases in the development of PE (not observed in other groups).

Premature delivery within gestation period up to 34 weeks was observed in almost every second pregnant woman in group 1, in 26.7% of cases - in the 2nd subgroup and not observed in Group 3; within the gestation period of more than 34 weeks - 40%, 60% and 28.6% of patients, respectively. In Group 1, timely delivery occurred only in 5.7% of pregnant women with gestational hypertension, in group 2 - in 13.3% of patients with gestational hypertension as well, in group 3, this indicator was 71.4%, which is significantly higher than in the first two groups.

Table 2 The condition of newborns depending on the method of prevention of HD in the gestation period

Indicators	**Groups of newborn with Bronchial hyperresponsiveness**					
	I group (n=35)		II group (n=15)		III group (n = 7)	
	GH (15) Total %	PE (20) Total %	GH (7) Total %	PE (8) Total %	GH (5) Total %	PE (2) Total %
Premature (22-37weeks)	13 86,7	20 100,0	5 71,4	8 100,0	1 20,0	1 50,0
Full-term (more than 37 weeks)	2 13,3	-	2 28,6	-	4 80,0	1 50,0
Newborns with IUGR	-	7 35,0	-	2 25,0	-	-
Weight of newborns	1886 (1300-3100)	1464 (670-2400)	2469 (1450-3300)	2068 (1040-2600)	3325 (2700-3600)	2750 (2300-3200)
Morbidity of Newborns	12 80,0	17 85,0	3 42,9	6 75,0	1 20,0	1 50,0
Perinatal mortality	1 66,7‰	6 300,0‰	-	1 125‰	-	-

The analysis of the delivery method showed that operative delivery in patients of the three groups was observed in 62.9%, 40% and 14.3% of cases, respectively, i.e., it reduced in the presence of the proposed preventive therapy by 4.4 times in compare with pregnant women who didn't receive drug prevention in preeclampsia and 2.8 times compared with pregnant women who received traditional preventive treatment. Moreover, the frequency of C-section during PE prevailed over the natural method of delivery only in pregnant women ($p < 0.05$) in Group 1, but it was the same in Group 2 and 3. In gestational hypertension, the frequency of operative and natural births was almost the same in group 1, in group 2 - natural delivery was observed 2.5 times more often, and the delivery happened natural in all pregnant women in group 3. Thus, we obtained statistically significant differences in delivery outcomes only in the group of pregnant women with PE.

For a more complete assessment of the effectiveness of the immunotherapy, we studied the condition of newborns in the study groups of pregnant women and the results are presented in Table 2. As a result of the provided work, a number of indicators in the state of newborns were found to improve based on the methods of therapy.

It was found that in gestational hypertension there is a statistically significant increase in the birth rate of full-term babies: in traditional treatment, the frequency of full-term newborns was 2.2 times higher ($p < 0.05$), and with the proposed preventive therapy, it is 6 times higher compared to newborns ($p < 0.01$), whose mothers did not receive preventive therapy, the effectiveness of immunotherapy for this indicator in comparison with traditional treatment was almost 3 times higher ($p < 0.05$). Similar differences were obtained in the analysis of the overall morbidity and neonatal weight indicators.

In PE of expectant mothers, the frequency of premature babies in Group 1 and 2, was almost identical, and in group 3 - 2 times lower ($p < 0.05$). There was observed an improvement in other indicators of the condition of newborns: decreasing in the frequency of newborns with IUGR by almost 1.5 times in the presence of generally accepted prevention ($p < 0.05$) and the absence of cases of IUGR in Group 3; decreasing in the overall morbidity of newborns.

4. Conclusion

The study found that traditional prevention reduces the incidence of HD in pregnancy by almost 2 times ($p < 0.05$), while the provided immunotherapy was more effective - 4 times ($p < 0.01$) in compare with pregnant women who did not receive preventive treatment. Our proposed prevention of HD using immunotherapy allowed to prevent severe forms of pathology and complications, such as IUGR and antenatal fetal death, significantly reduced frequency of premature, and operative births, indicators of perinatal mortality and general morbidity of newborns, etc. Pregnant women with various risk factors for PE are recommended to undergo treatment and preventive measures from the end of the first trimester of gestation throughout the gestational period, which contributes to a significant improvement in pregnancy outcomes for both the mother and fetus. The provided treatment method allowed reducing birth rate of premature babies by 3.3 times in comparison with patients without treatment and by 3 times when compared with pregnant women who received conventional methods of prevention. The indicators of the overall morbidity of newborns decreased by 1.5 times - in patients with conventional treatment compared with pregnant women without treatment, 3 times in the surveyed by a new technique. Perinatal mortality in pregnant women with traditional therapy decreased almost by 3 times compared to pregnant women who had not received preventive measures and was not observed in any patient with complex preventive therapy with immunotherapy.

Compliance with ethical standards

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Disclosure of conflict of interest

The Authors declare no conflict of interest.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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