GESTOSIS

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Gestosis is one of the most serious pregnancy complications responsible for a significant rate of maternal and perinatal morbidity and mortality.

Gestosis pathogenesis as well as prophylaxis and pathogenetically based treatment have not been determined finally despite continuous attention to this problem in whole world. Absence of unique classification of this pathological condition makes it difficult to solve this problem. The International Society for the Study of pregnancy-induced hypertension proposes following classification: pregnancy-induced hypertension, preeclampsia (hypertension with proteinuria), except edema. Society for studying pregnancy toxemia is based on the fact that in experimental laboratory studies preeclampsia could be induced in pregnant rats by injection of a small dose of endotoxin.

Some scientists in Japan and our country follow this classification.

International Gestosis Organization uses the term of OPH-gestosis e.g. edema, proteinuria and hypertension.

There are a lot of theories of gestosis development but not any one could explain all questions in borders of each theory.

Risk factors for gestosis development are adopted by majority of scientists.

Endorcrine pathology is one of unfavorable backgrounds for gestosis development. According our data, patients with metabolic disorders may be identified as high risk for gestosis in 42% with the prevalence of diabetes mellitus (20%). Nowadays many researchers consider increased insulin resistance among the predisposed factor to gestosis.

In the research of gestational diabetes we have demonstrated that frequency of gestosis depended on initial serum glucose level. Thus, initial serum glucose level of 5-6 mmol/L was associated with gestosis in 12,7%, serum glucose levels of 7-8 mmol/L correlated with 28,9% frequency of gestosis. High l initial serum glucose level (11-12 mmol/L) accompanied by gestosis development in 55.6% of patients.

Thus, positive correlation between initial serum glucose level and gestosis frequency testifies for diabetes compensation by insulin administration.

Renal pathology is another important risk factor of gestosis. According to Prof. Pipkin's data, up to 80% of primegravidae with gestosis suffer from renal diseases proved by renal biopsies in those patients.

In the attempt to reveal the cause of gestosis we assessed pathomorphological changes in nephrobioptic specimens of 20 women with the history of severe gestosis and perinatal losses. Samples were taken in different periods after delivery (from 8 days to 1,5 years) in patients whose pregnancy was complicated by severe gestosis (including preeclampsia and eclampsia in 25% and 5%, accordingly). Due to severe gestosis pregnancy in 70% cases was terminated preliminary (in 25% cases up to 28 weeks of gestation and in 45% up to 37 weeks of gestation). Perinatal losses were noted in 45% of patients. Nephrobiopsy was performed in the specialized laboratory of Research Institute of Transplantology and Artificial Organs.

As evidence by our investigations, pathological renal changes were found in 41% of studied bioptic samples from gestosis patients. Besides this glomerular capillary endotheliosis was the most common lesion.

The most interesting find of this study was high frequency (93%) of different types immunoglobulin (IgG, IgM, IgA) deposits in nephrobioptic specimens in patients with the history of severe gestosis even in absence of renal morphological changes. Our findings have suggested that circulating immune complexes fixed in different tissues and organs can cause functional and structural lesions and play important role in the gestosis patogenesis.

Our study of women with transplanted kidneys has become a confirmation of this suggestion. We examined 35 pregnant patients with transplanted kidney performed because of terminal stage of chronic renal failure. Before the transplantation all patients underwent long-term dialysis (hemodialysis and peritoneal dialysis with the duration of 18 and 14 month, respectively). After transplantation all women were given immunosuppressive therapy that was continued during pregnancy (except cytostatics such as azathiaprine).

We noted that despite severe renal pathology only in two cases among 35 patients with transplanted kidney pregnancy was complicated by mild gestosis. 33 patients were delivered at 33-37 weeks of pregnancy, all babies born alive (2 women had stillbirth before 24 weeks of gestation). There is a reasonable question: why pregnant

patients with severe renal diseases, after renal transplantation due to chronic renal failure did not have such complication as gestosis. Meanwhile it is known that gestosis develops in women with preexisting renal disease in 40-60%.

Trying to answer this question we paid attention on the fact that all recipients received immunosuppressive therapy including glucocorticoids during pregnancy.

As has been established immune disturbances play an important role in gestosis as immunopathological mother's reactons might be potentially destructive for fetus. From these positions some authors consider gestosis is a consequence of invasion of fetal antigens into maternal blood circulation. These antigens cause maternal reactivity disturbances resulted in changed immunological reactions.

We hypothesized that immunosuppressive therapy has allowed us to prolong pregnancy in women with transplanted kidney avoiding such a serious complication as gestosis. To support this theory we retrospectively analyzed medical cases of pregnant patients with different pathology pyelonephritis (n=6), hypertension of pregnancy (n=10), edema (n=10). All of them were given glucocorticoids as a part of a complex therapy. It is interesting to note that none of them developed severe or even moderate gestosis that could be a confirmation of our theory about the importance of immunosuppressive therapy for gestosis prophylaxis. Some authors (Martin) carrying out prophylaxis of fetal distress-syndrome by glucocorticoids in women with severe gestosis have also paid attention at improvement of patients' state and possibility of pregnancy prolongation (2 and more weeks) after such therapy. So, immunosuppressive therapy may be an effective method of gestosis prophylaxis and treatment.

The received data confirm the important role of immune disturbances in gestosis development.

Undoubtedly, gestosis is a pathology associated with implantation that pathological mechanisms are formed at early gestation and only pregnancy termination could interrupt the pathologic process. Some investigators consider that immunological and biological disturbances in system mother-placenta-fetus play the crucial role in gestosis. Nowadays, many research works have been focused on imbalance of Th1 and Th2 type immunity.

T-cell leucocytes and macrophages dysfunction during pregnancy could lead to improper cytokine regulation. Elevated tumor necrosis factor-α (TNF) and interleukin-2, interleukin-6 (IL-2, IL-6) levels are found in gestosis. In our study all

this cytokines were increased depending on gestosis severity. We registered the elevation of these immune markers from 16-24 weeks of gestation, e.g. before clinical signs of gestosis. So, these cytokines could be used as early markers of gestosis.

Presence of a small amount of TNF-α and trace quantities of IFN-γ in blood of women with normal pregnancy indicates adaptation process of maternal immune system. From the other side, expressed elevation of TNF-α and IFN-γ in gestosis patients may reflect an abnormal immune activation. This fact is in accordance with other authors' data of mechanisms of gestosis development with abnormal activation of maternal immunity against fetus-allograft. Maternal immune system reacts with alloantigens of fetus tissues in the case of insufficient immunosupression, resulting in the maternal immune response analogical to fetus rejection reaction, due to macrophage and lymphocyte activation with consequent TNF α release. Japanese researchers (Opashi) evaluate TNF α as rejection mediator. The important confirmation in favor of immunological disorders in gestosis is the fact of its high frequency in primigravidas. Pregnancy followed condom contraception is complicated by gestosis in more cases. The transfusions of father's blood, containing father's antigens or long period of sexual contacts of women with the partner before the pregnancy decrease the risk of gestosis for the future pregnancy. For this reason we apply the immunotherapy of the pregnant women with the husband's lymphocytes for gestosis therapy.

Endothelial dysfunction is the central mechanism of gestosis pathogenesis. Misbalance of vasodilator and constrictor also plays an important role in gestosis development, particularly in uteroplacental and renal blood circulation. Disturbed vasodilator/constrictor balance is considered to be one of the central points in gestosis development and explain different clinical signs.

Nitric oxyde (NO) is one the most significant endogenous vasodilators. In experimental study we have found that NO concentration was twofold decreased in pregnant rats with pregnancy induced hypertension compared to healthy pregnant rats. It has been established in our research that NO is produced in circadian rhythm. Besides low NO concentration patients with gestosis demonstrated decreased plasma ability for NO transport revealed from early gestation.

It has been known that gestosis is characterized by deficiency of essential fatty acids (ω-6 and ω-3 fatty acids) - direct precursors of different classes' eicosanoids. In our work in gestosis patients we observed eicosapentaenoic acid decreasing accompanied

by considerable TxB_2 increasing (1.5 times higher than in normal pregnancy). Marine fish oil in the complex gestosis therapy contributes to decrease TxB_2 and TxA blood levels and increase of eicosapentaenoic acid level as well as diminish hypercoagulation.

The central point of gestosis pathogenesis takes the endothelial dysfunction, which based from hyperhomocysteinemia.

In non-pregnant women hyperhomocysteinemia results from genetic (defects of metilentetragidrofolatreductasa (MGTRF) and other enzymes of metionin-homocystein methabolism) and dietary factors (folat, B6, B12 defficiency).

In healthy pregnant women serum homocystein was significantly lower (3,5mmol\l), than in non-pregnant controls. In patients with gestosis it's concentration was statistically higher (5,3+_0,3 mmol/l) than in healthy pregnant women. This difference kept from 29 up to 40 weeks of gestation. We found that severity of gestosis positively correlate with homocystein concentration:4,7+-0,3 mcmol/l in mild gestosis, 5,0+-0,4mcmol/l in moderate and 7,7mcmol/l in severe gestosis.

The direct positive correlation of homocystein and fibronectin in blood serum ($r=0,7$; $p<0,001$) has been found, what indicates on the connection of enhanced homocystein level and endothelium dysfunction.

Thus, we established, that homocystein concentration in the III trimester of normal pregnancy (3,5+-0,1 mkM\l) is statistically lower than in non-pregnant women. Significant increase of homocystein level accompanies gestosis development in compare to normal pregnancy and exists the direct positive correlation with gestosis severity. Homocystein level increase is connected with endothelium dysfunction. Women with homocystein level (more than 7mcM\L) suffer from more severe gestosis and poor perinatal outcomes.

Folat-dependent enzyme – metilentetragidrofolat-reductaza (MGTRF) is involved in homocystein methabolism. In healthy pregnant women high thermolability of enzyme caused by it's mutation leads to enzyme decreased activity, that was revealed in our study in 29,6% cases. In all cases mutation occurred in one chromosome. Mutation 677(C-T) have been found statistically more often in women with gestosis (64% of cases) ($p<0,05$). Homozygote form of this mutation happened in 6,3% and geterozygote form – in 57,8%.

Rate of 677(C-T) MTHFR mutation was 55,9%, 67,7% and 77,8% in patients with mild, moderate and severe gestosis positively correlated with its severity.

Folic levels were significantly lower in serum of 677(C-T) MTHFR mutation patients compared with pregnant women with normal genotype. Folate levels were 4,3±1,6 ng/ml and 2,4±0,5 ng/ml in gestosis patients with normal genotype and 677(C-T) MTHFR mutation, accordingly. Normal folate levels for pregnancy is higher then 5 ng/ml.

Folic acid participates in regulatory processes of protein and nucleic acids synthesis accelerates reparative processes in damaged endothelium. We noted negative correlation between erythrocyte folic level and plasma fibronectin ($r=-0,4$, $p<0,05$).

In our study erythrocyte folate level was significantly lower in patients with moderate and severe gestosis, compared with control one, so there was a trend to negative correlation between erythrocyte folate level and gestosis severity.

Unfortunately, our data demonstrated that intake of polyvitamin complexes, containing 1 mg or 0,8 mg of folic acid, didn't lead to significant increase of folic acid levels both in serum and erythrocytes. Polyvitamin intake also didn't influence blood homocystein levels (5,2±0,4 mcM/l and 5,4±0,4 mcM/l with or without polyvitamin intake, accordingly).

So our data showed folic deficient practically in all gestosis patients that wasn't compensated by use of traditional vitamin doses. The most severe gestosis forms were associated with highest folic deficient. Presence of MTHFR mutation leads to significant decrease of serum folate levels. Perhaps, increase effectiveness of gestosis treatment needs higher folic acid doses (>1 mg/day) that could accompanied by positive influence on vessel endothelium and decreasing of blood homocystein levels.

Thus, we propose that following directions could be developed in treatment of gestosis:

1. immune-cytotherapy,IG therapy
2. Use of glucocorticoids (prednisolon, metipred)
3. Folic acid supplementation
4. Antiaggregants and anticoagulants.
5. Polyunsaturated lipid acids supplementation.