

The Significance of Angiogenic Growth Factor in the Pathogenesis of Gestosis in Pregnant Women with Varicose Disease

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Recently, a close relationship between angiogenesis processes, growth factor activity in vascular abnormalities, and gestosis was revealed. In the present study, the dynamics of serum vascular endothelial growth factor during pregnancy was studied in patients with varicose disease with and without gestosis and in healthy women. The level of vascular endothelial growth factor increased during normal pregnancy, but decreased in gestosis. In pregnant patients with varicose disease, a less pronounced increase in this parameter was observed in comparison with that in healthy women.

Key Words: *vascular endothelial growth factor; gestosis; varicose disease; pregnancy*

The search for early markers of gestosis is an important problem of modern obstetrics; among these markers are growth factors playing an important role in the development of placenta.

Favorable course and outcome of gestation largely depend on implantation and placentation. Successful implantation and further development of the placenta are determined by intricate angiogenesis process regulated by growth factors, which, on the one hand, stimulate angiogenesis and increase vascular permeability in the placental bed and on the other, regulate (through the autocrine mechanism) invasion, differentiation, and metabolic activity of the trophoblast during placentation.

Pathological invasion of the trophoblast in the spiral arteries leads to complications of pregnancy, *e. g.* gestosis. Two peaks of invasive activity are known: during weeks 8-10 of gestation (the first

wave of the extravillous cytotrophoblast invasion into the placental bed) and during weeks 16-18 (the second wave, when the extravillous cytotrophoblast penetrates into the myometrial segments of spiral arteries transformed into uteroplacental arteries). Abnormalities of gestation restructuring of the placental bed spiral arteries are caused by incomplete or insufficient invasion of the extravillous cytotrophoblast, its activity being regulated by local growth factors [1,12].

Vascular endothelial growth factor (VEGF), known also as vascular permeability factor or vasculotropine [9,11], is one of the best studied growth factors. The role of VEGF and its receptors during the development of placenta was experimentally proven [6].

Gestosis can be regarded as an antiangiogenic condition developing as a result of imbalance between angiogenic and antiangiogenic factors. The VEGF and its receptors are the key factors in the development of this condition [3,10].

Varicosity is one of prevalent diseases of the peripheral vessels in pregnant women associated with valvular incompetence and bloodflow disorder.

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ders. A relationship between VEGF level and severity of varicose disease was reported; the maximum increase in the content of this factor was observed in patients with trophic lesions of the skin [8].

Here we studied the clinical diagnostic role of VEGF in the pathogenesis of gestosis and varicose disease in pregnant patients

MATERIALS AND METHODS

Eighty-one pregnant women were examined. Group 1 consisted of 46 pregnant patients with varicose disease, group 2 of 7 pregnant patients with varicose disease and clinical manifestations of gestosis, and control group comprised 28 healthy pregnant women.

Gestosis was diagnosed by edemas, blood pressure above 140/90 mm Hg, and proteinuria >0.3 mg/day. The severity of varicose disease was evaluated by CAEP classification.

The level of VEGF was measured throughout all trimesters of pregnancy (before 12 weeks, on weeks 13-26, and from weeks 27-40). The blood was collected after overnight fasting from the ulnar vein under standard conditions. Serum samples were stored at -70°C before analysis. The concentrations of VEGF (in pg/ml) were measured by ELISA (R&D Systems).

The results were processed using Statistica software. The significance of differences between the groups was evaluated using ANOVA software and Kruskal—Wallis and Mann—Whitney tests, Student's *t* test with Bonferroni's amendment, and by Wilcoxon's test. The results were presented as $M \pm SD$. The differences were considered significant at $p < 0.05$.

RESULTS

According to ELISA results, serum VEGF level in normal pregnancy increased in proportion to gestation term: 16.94 ± 4.83 pg/ml during the first trimester, 23.56 ± 9.40 pg/ml during the second, and 24.94 ± 1.20 pg/ml during the third trimester (Fig. 1). The increase in VEGF level was irregular, the peaks coinciding with trophoblast invasion waves 1 and 2 (weeks 8-9 and 16-18).

The mean values of VEGF were lower in pregnant patients with gestosis and varicose disease during trimesters II and III in comparison with healthy pregnant women (15.25 ± 3.40 pg/ml and 12.48 ± 3.10 pg/ml, respectively); VEGF level inversely correlated with gestosis severity ($r = -0.5520$, $p < 0.05$), that is, serum VEGF level was

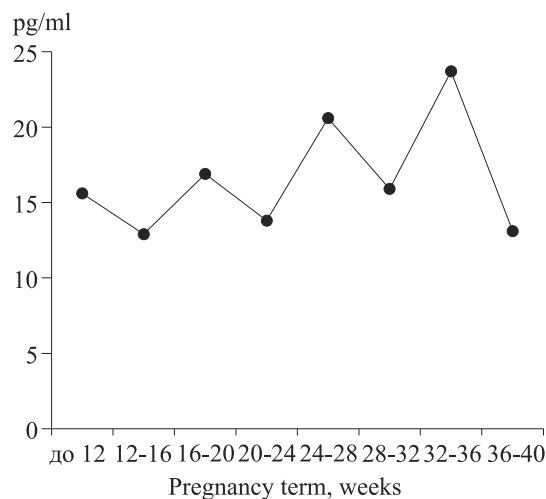


Fig. 1. Dynamics of VEGF production throughout pregnancy in healthy pregnant women.

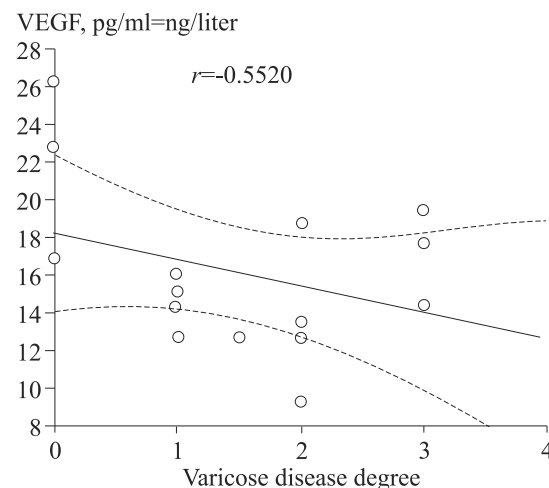


Fig. 2. Correlation between VEGF and gestosis severity. Here and in Fig. 3: direct line shows 95% confidence interval.

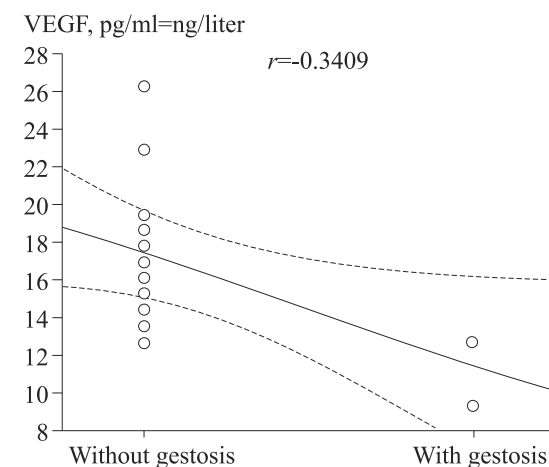


Fig. 3. Correlation between VEGF and degree of venous insufficiency.

lower in pregnant patients with clinically manifest gestosis (Fig. 2).

A trend to an increase in the mean VEGF level with the progress of pregnancy was observed, but this increase was statistically insignificant. In addition, a slight correlation between VEGF level and degree of venous insufficiency was noted (Fig. 3).

We conclude from these results that VEGF, one of the priority activators of placental development, differentiation, and invasion, plays the key role in the development of pregnancy abnormalities. Our findings and published data indicate an increase of VEGF level at later terms of normal pregnancy. The reduction of VEGF level was noted in pregnant women with gestosis, indicating disorders in the vascular development of the placenta and insufficient trophoblast invasion underlying the pathogenesis of gestosis.

Hence, VEGF level can serve as an early prognostic marker of gestosis development long before its clinical manifestation, which is important for its prevention and early therapy.

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