



COGEN

Preconception, Preimplantation and Prenatal Genetic Diagnosis (CoGEN)

EFFECT OF PRECONCEPTION TREATMENT OF L-5-METHYLTETRAHYDROFOLATE, VITAMIN D AND ARGININE AT CLOMIPHENE-RESISTANT WOMEN WITH POLYCYSTIC OVARIAN DISEASE AND MTHFR POLYMORPHISMS

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ABSTRACT

Ovulatory disturbance and infertility is a key diagnostic feature of polycystic ovarian syndrome (PCOS) in the pathogenesis of which, together with hormonal and metabolic disorders an important place is occupied by genetic defects in folate cycle enzymes methylenetetrahydrofolate reductase (MTHFR).

OBJECTIVE: of the study is to evaluate the efficacy of treatment of combination therapy with L-5-methyltetrahydrofolate, vitamin D and arginine at clomiphene-resistant women with polycystic ovarian disease and MTHFR polymorphisms

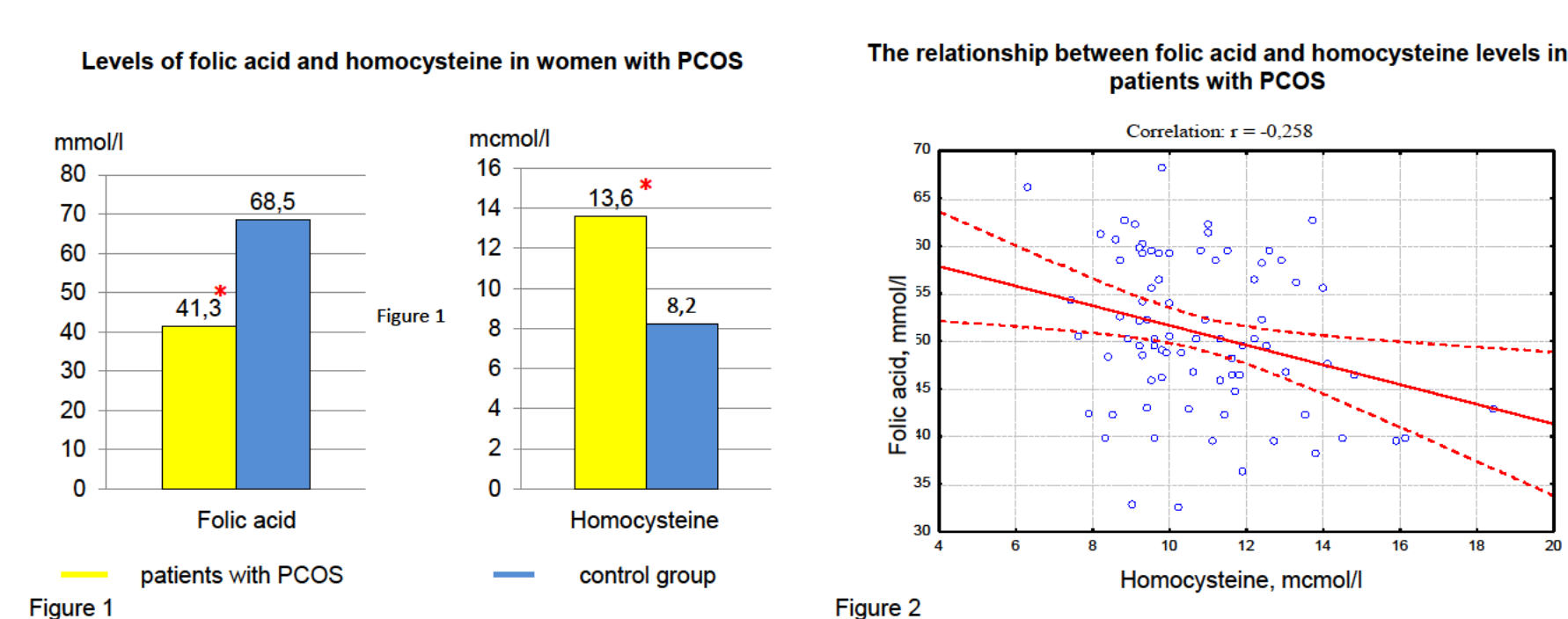
PATIENTS AND METHODS: 80 women undergoing were enrolled with PCOS, MTHFR C677T and A1298C polymorphisms and in clomiphene resistance. The study group was treated with L-5-methyltetrahydrofolate 800 mcg, cholecalciferol (4000 IU) daily for 24 weeks; from 1 to 4 weeks and from 13 to 17 patients received arginine 3g daily; after 12 weeks of therapy, ovulation was stimulated with clomiphene citrate at a dose of 50 mg 3 menstrual cycles. The level of folic acid, homocysteine, vitamin D, endothelin-1, vascular endothelial growth factor, NO_x and arginine were determined before and after 12 and 24 weeks of therapy. The maximum systolic blood flow velocity and the resistance index of intraovarian vessels were assessed. Ovulation frequency was evaluated as primary result clinical pregnancy as secondary outcomes.

RESULTS: Treatment significantly increase levels of folic acid, cholecalciferol, arginine and decrease levels of homocysteine, endothelin-1, vascular endothelial growth factor, NO_x after 12 weeks of therapy. During the next 12 weeks of therapy the dynamics of the studied parameters was absent. There was a decrease the maximum systolic blood flow velocity and resistance index of intraovarian vessels which indicated an improvement in intraovarian hemodynamics. When using clomiphene citrate, ovulation was observed in 54 (67,5%) patients and 34 (42,5%) patients experienced pregnancies.

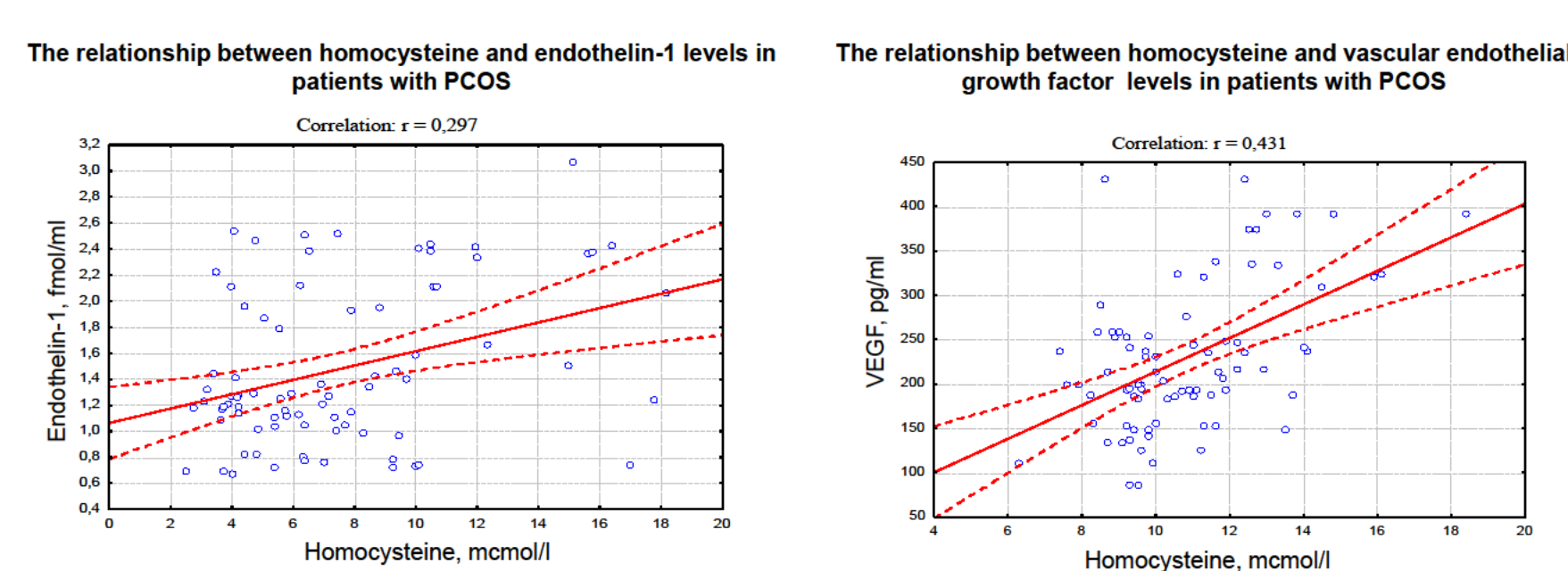
CONCLUSIONS: The supplementation of L-5-methyltetrahydrofolate, vitamin D and arginine in the first 3 months before induction ovulation clomiphene citrate and in the further 3 months during ovulation stimulation could represent innovative support for all those women with PCOS and MTHFR polymorphisms.

RESULT

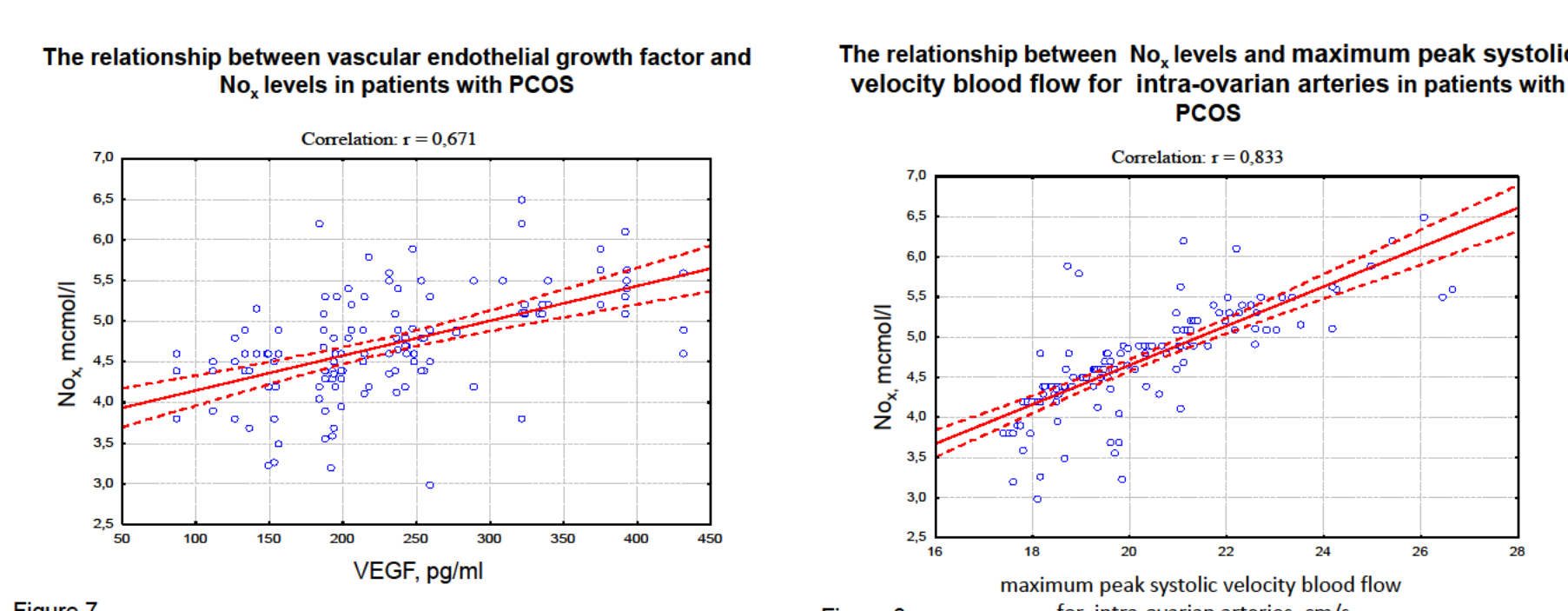
The study was conducted on 80 clomiphene-resistant patients with PCOS and MTHFR polymorphism. The concentration of folic acid in the blood serum of these examined was significantly lower than in the group of healthy women (Figure 1). It is known that folic acid is involved in the metabolism of homocysteine. The existing correlation between these indicators indicates that folic acid deficiency is a predictor of the formation of hyperhomocysteinemia (Figure 2).



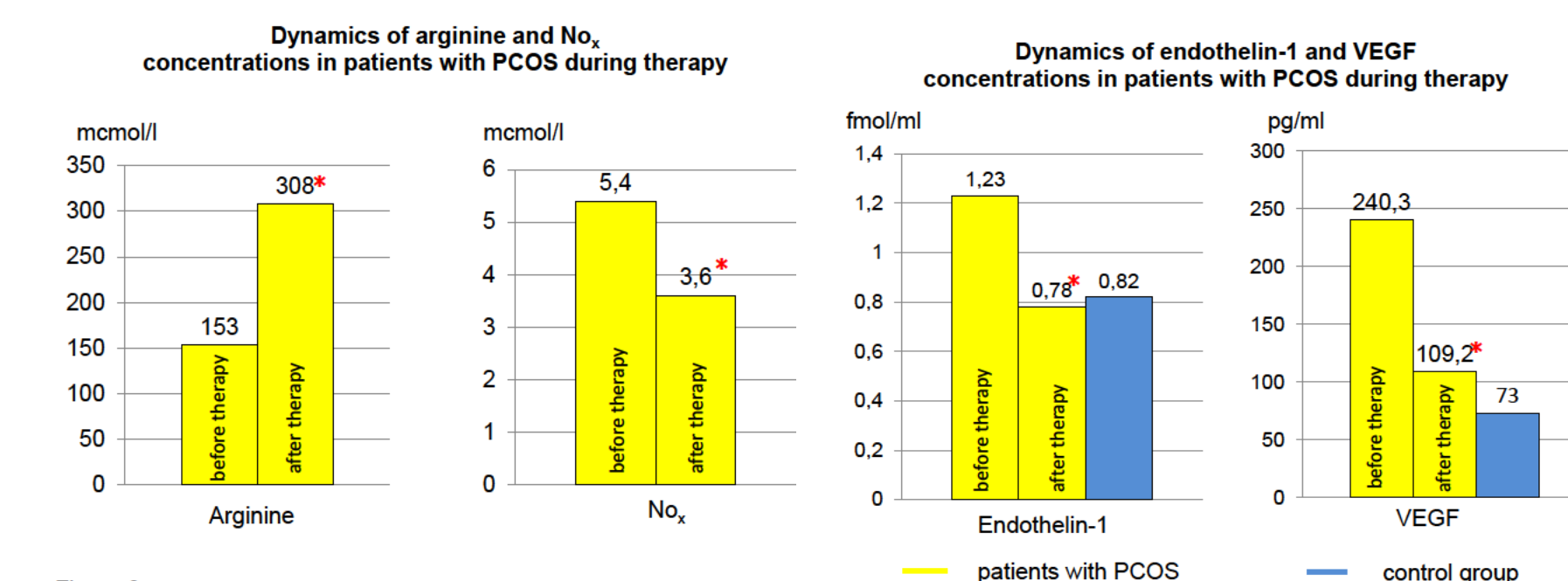
Hyperhomocysteinemia which exists in patients with PCOS is a factor in the formation of endothelial dysfunction, as evidenced by positive correlations between the levels of homocysteine, endothelin-1 and vascular endothelial growth factor (VEGF) (Figure 5,6).



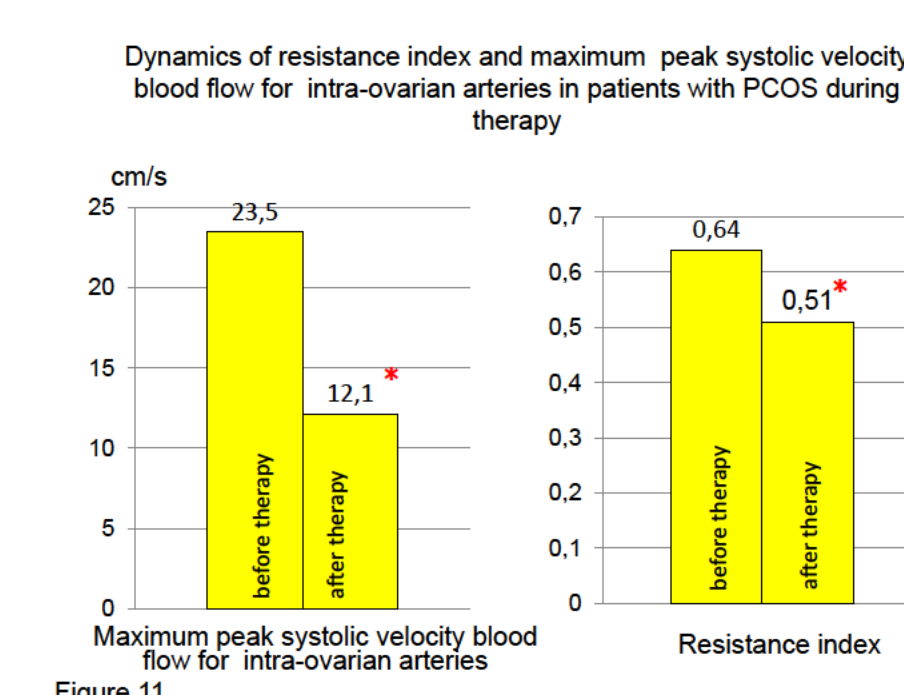
A direct correlation between indicators of vascular endothelial growth factor and nitric oxide metabolites indicates an imbalance in the endothelial control of vascular tone (Figure 7,8).



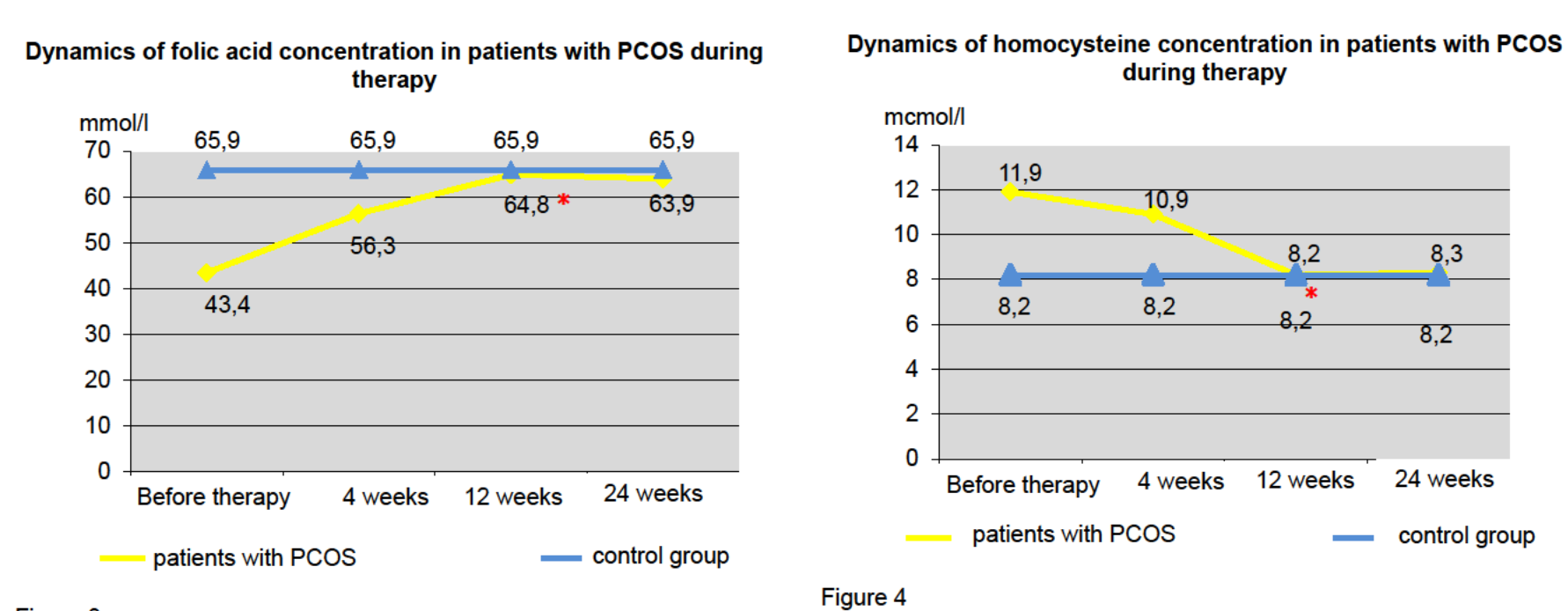
Arginine is the only substrate for the NO synthetase enzyme, which acts as a catalyst in the synthesis of nitric oxide in the cells of the vascular endothelial membrane. The L-arginine therapy conducted in this study led to an increase in the concentration of arginine, a decrease in the levels of nitrate-nitrites, endothelin-1, vascular endothelial growth factor which accordingly was associated with an improvement in endothelial function (Figure 9,10).



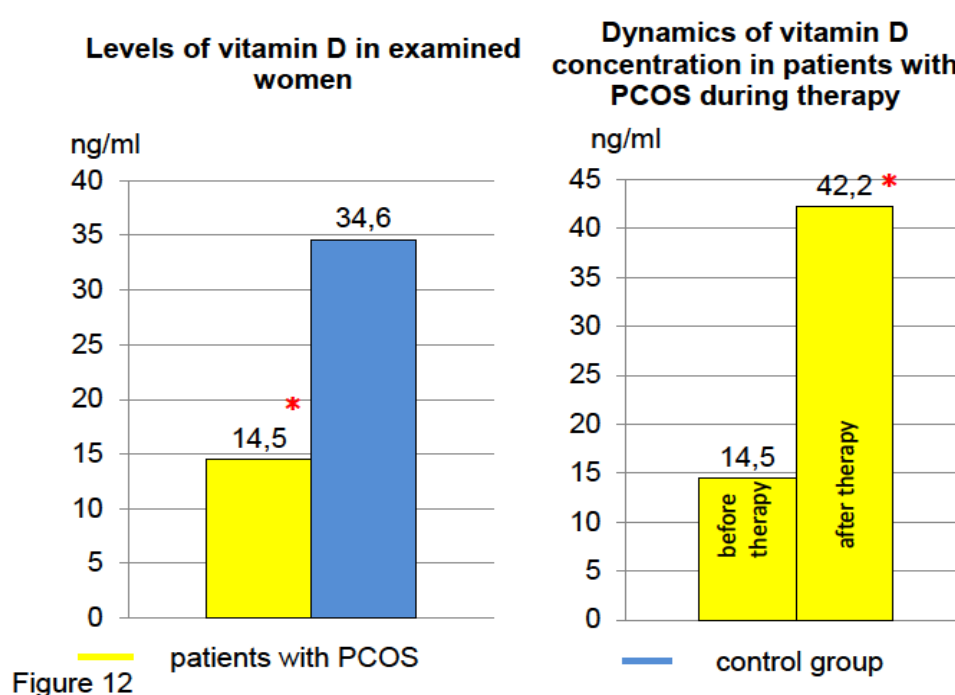
There was a decrease the maximum systolic blood flow velocity, a decrease in the resistance index of intraovarian vessels which indicated an improvement in intraovarian hemodynamics (Figure 11).



Based on the above, the appointment of L-5-methyltetrahydrofolate 800 mcg daily was pathogenetically justified. Against the background of therapy the level of folic acid and homocysteine normalized during the first 12 weeks and there were no changes in this indicator in the next 12 weeks. An increase folic acid levels above the reference normal values during therapy was not registered (Figure 3,4).



High levels of homocysteine in patients with PCOS were negatively correlated with serum vitamin D concentrations. Vitamin D levels were significantly lower than in the control group, consistent with deficiency indicators. The appointment of cholecalciferol led to the normalization of vitamin D levels during the first 12 weeks and in the next 12 weeks there were no changes in this indicator (Figure 12).



During therapy of L-5-methyltetrahydrofolate, vitamin D and arginine the appointment clomiphene citrate, ovulation was observed in 54 (67,5%) patients and 34 (42,5%) patients experienced pregnancies.

CONCLUSION

The supplementation of L-5-methyltetrahydrofolate, vitamin D and arginine in the first 3 months before induction ovulation clomiphene citrate and in the further 3 months during ovulation stimulation could represent innovative support for all those women with PCOS and MTHFR polymorphisms.

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