Trophoblastic β_1-Glycoprotein and Hemostasis System in Pregnant Women with Antiphospholipid Syndrome

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Clinical and laboratory studies were carried out in 38 pregnant women with antiphospholipid syndrome. Increased functional activity of platelets and decreased protein-producing function of the placenta were observed starting from the early terms of gestation. These disorders were followed by the development of hypercoagulation in the plasma component of hemostasis, appearance of intravascular blood clotting markers, and inhibition of AT III and protein C. This led to the progress of disorders in the microcirculatory bed, fetoplacental insufficiency, decrease in trophoblastic β_1-glycoprotein level, chronic hypoxia, and fetal death. Infection accelerated this process. Measurements of trophoblastic β_1-glycoprotein every 2 weeks help to diagnose fetoplacental disorders, predict the course of pregnancy, and evaluate the efficiency of drug therapy.

Key Words: *pregnancy; trophoblastic β_1-glycoprotein; antiphospholipid syndrome; hemostasis system; lupus anticoagulant*

Antiphospholipid syndrome (APS) associated with circulation of lupus anticoagulant (LA) is a common manifestation of immune aggression towards the vascular and platelet components of hemostasis. The role of antiphospholipid antibodies (APA) in the mechanisms of pregnancy abnormalities and intrauterine growth retardation is now proven. The pathogenetic effect of APS is realized through microcirculatory disorders in the mother-placenta-fetus system resulting from generalized involvement of the vascular wall and activation of intravascular clotting [1,2,5-8,11]. APA directly interact with syncytiotrophoblast and inhibit fusion of trophoblast cells [10]. Evaluation of functional activity of the trophoblast is important for studies of processes associated with differentiation of chorion cells. Trophoblastic β_1-glycoprotein (TBG) is a marker of the fetal placenta and is produced by cyto- and syncytiotrophoblast cells. This marker is used in clinical practice for the diagnosis of pregnancy abnormalities, trophoblastic tumors, and for monitoring of the efficiency of treatment of these conditions [9,12].

We investigated the state of the hemostasis system and TBG synthesis in women with APS during the first half of pregnancy.

MATERIALS AND METHODS

Clinical and laboratory studies were carried out in 38 pregnant women aged 22-35 years with APS and habitual miscarriages. The study group included women with LA first detected during the current pregnancy and women with repeatedly detected LA receiving hormone therapy before pregnancy. Highly positive, positive, and low positive coagulation tests with LA and changes in the hemostasis served as criteria of immunopathological process. Hemostasis system and LA were studied using commercial reagents (Tekhnologiya-Standart); TBG concentration in the capillary blood serum was measured as described previously [3,4]. Antibodies to chorionic gonadotropin were determined using IFA-Antibody to CG kits and antibodies to thyroglobulin by the passive hemagglutination test with commercial kits (Preparat Firm).

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The significance of differences was evaluated using Student's *t* test, the differences were considered significant at $p<0.05$.

RESULTS

At weeks 6-8 of gestation most patients receiving drug therapy had highly positive, positive, and low positive reaction to LA (Fig. 1, *a*), which favored pronounced blood clotting disorders in these patients. High incidence of hemostasis disorders is worthy of note (Fig. 1, *b*). Hyperfunction of the platelet component of the hemostasis system was observed in 73.6% women; markers of intravascular blood coagulation were detected in 44.7% examinees, which indicated manifestation of chronic disseminated intravascular coagulation. Moreover, the time of euglobulin clot lysis increased to 269.8±15.9 sec (*vs.* 221.0±23.3 sec in normal). The appearance of antibodies to thyroid factors (in 26.3% women) and chorionic gonadotropin (in 34.2% women) increased the risk of implantation and placentation disturbances. Drug therapy stabilized autoimmune processes by weeks 16-20 of gestation (Fig. 1, *a*). Positive changes in TBG level were observed in women with negative and low positive reaction to LA. Despite stabilization of TBG content, the mean values were lower than in healthy pregnant women at the corresponding terms (45.2±3.5 *vs.* 52.7±6.3 μg/ml). In 9 women TBG content slightly increased, while in 5 no changes were observed. Drug therapy combined with plasmapheresis (3 patients) or immunoglobulins (4 patients) resulted in reversion of the results. By week 20 of pregnancy only 2 patients with highly active autoimmune processes showed low positive reaction to LA. Positive changes in TBG level and stabilization of hemostasis parameters were observed in 5 women.

Hence, evaluation of hemostasis parameters revealed pronounced hyperactivity of platelets (time of aggregation 11±2 *vs.* 16±2 sec in normal) in pregnant women with positive reaction to LA as early as in the first trimester. By week 20 in 18.4% women receiving drug therapy abnormal activity of platelets was associated with hypercoagulation not characteristic of this term (shortening of activated recalcification time by 12% and activated partial thrombin time by 6% compared to healthy pregnant women). Prothrombin index increased to 96.20±1.14% (*vs.* 93.8±2.8% in normal) and fibrinogen concentration increased to 3.38±0.12 g/liter (*vs.* 3.19±0.31 g/liter in normal). Markers of intravascular coagulation (soluble fibrin-monomer complexes, 4.8±0.8 *vs.* 3.5±0.5 mg/100 ml in normal) and reduced activities of antithrombin III (79.6±2.3 *vs.* 95.0±2.8% in normal) and protein C (80.2±6.3 *vs.* 106.8±6.8% in normal) were detected in the majority of examined women. On the other hand, by week 20 of gestation 21% LA-positive women receiving a course of therapy had signs of hypocoagulation: prolonged activated partial thrombin time and activated recalcification time and decreased prothrombin index. These changes were associated with decreased content of antithrombin III (to 80.2±1.8%) and protein C (81.5±4.3%) and increased content of soluble fibrin-monomer complexes. In other LA-positive patients (n=23) controlled antithrombotic therapy stabilized hemostasis (prothrombin index increased to 92.10±0.98%, fibrinogen level to 3.12±0.11 g/liter, platelet aggregation and content of soluble fibrin-monomer complexes decreased, activities of antithrombin III and protein C increased by 15 and 28%, respectively. Prolonged remissions (negative tests for LA) were observed in 17 patients by week 20.

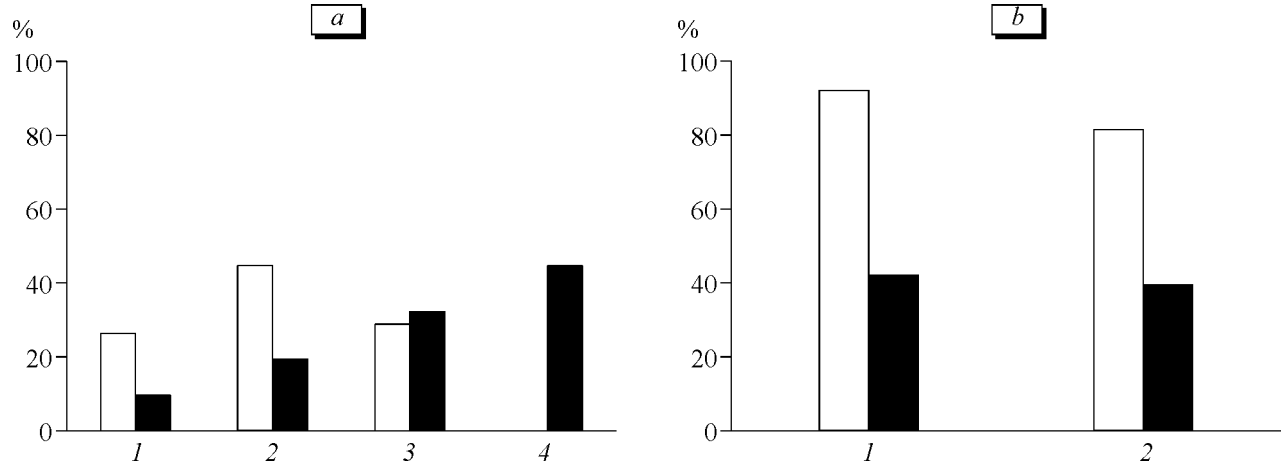

Fig. 1. Distribution of pregnant women with antiphospholipid syndrome depending on the reaction to lupus anticoagulant (*a*) and disorders in hemostasis and synthesis of trophoblastic β_1-glycoprotein (*b*) before (open bars) and after therapy (dark bars). *a*: *1*) highly positive; *2*) positive; *3*) low positive; *4*) negative reaction to lupus anticoagulant; *b*: disorders in: *1*) hemostasis system; *2*) synthesis of trophoblastic β_1-glycoprotein.

The level of TBG was much lower in LA-positive women with viral infections, which was presumably due to partial death of the trophoblast. Actively proliferating trophoblast tissue serves as the target for virus replication. Virus multiplication leads to death of trophoblast cells and inhibition of TBG biosynthesis and transport.

Hence, measurements of TBG help to diagnose even minor changes in the syncytium. The content of TBG serves as an indirect indicator of the state of the fetoplacental system. It warns of disorders in the uteroplacental blood flow augmenting imbalance in maternal hemostasis provoked by antibodies to LA. Measurements of TBG every 2 weeks help to predict the course of pregnancy and evaluate the efficiency of combined drug therapy.

REFERENCES

1. Kh. Abbasi and A. L. Mishchenko, *Akush. Ginekol.*, No. 6, 17-20 (1996).
2. A. A. Agadzhanova, *Ibid.*, No. 3, 6-8 (1999).
3. R. N. Bogdanovich and T. A. Berestovaya, *Lab. Delo*, No. 9, 43-45 (1990).
4. R. N. Bogdanovich, I. V. Chikalovets, and T. A. Berestovaya, *Pressing Problems of Female Reproductive Health* [in Russian], Vladivostok (1999), pp. 231-240.
5. A. D. Makatsariya, A. B. Raskurazhe, A. L. Mishchenko, *et al.*, *Akush. Ginekol.*, No. 3, 6-9 (1993).
6. A. D. Makatsariya and V. O. Bitsadze, *Ibid.*, No. 2, 62-67 (1999).
7. A. D. Makatsariya, *The Antiphospholipid Syndrome in Obstetrical Practice* [in Russian], Moscow (2000).
8. G. E. Sapina and A. L. Mishchenko, *Akush. Ginekol.*, No. 1, 30-33 (1999).
9. Yu. S. Tatarinov and V. N. Masyukevich, *Byull. Eksp. Biol. Med.*, **69**, No. 6, 66-68 (1970).
10. W. H. Kutteh, *J. Reprod. Immunol.*, **3**, 151-171 (1997).
11. N. S. Rote, *Immunology of Reproduction*, Ed. R. K. Naz, New York (1993), Vol. 8, pp. 146-167.
12. Y. S. Tatarinov, N. V. Mesnyankina, D. M. Nikulina, *et al.*, *Int. J. Cancer*, **14**, 548-554.