EXPERIMENTAL METHODS FOR CLINICAL PRACTICE

Blood Clotting Disorders in Gestosis and Pulmonary Mechanisms of Their Compensation

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Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny,* Vol. 132, No. 12, pp. 669-671, December, 2001
Original article submitted September 25, 2001

We studied blood coagulation system in women with uneventful pregnancy and with gestosis and evaluated the hemostasis-regulating role of the lungs in pregnancy and gestosis. We found a correlation between disorders in the pulmonary fibrinolytic function and severity of gestosis, and demonstrated the role of compensatory pulmonary mechanisms in the maintenance of adequate microcirculation in maternal organism and in the mother-placenta-fetus system. Prognostic and diagnostic criteria of gestosis and its complications are proposed.

Key Words: *hemostasis; regulation; lungs; pregnancy; gestosis*

Late gestosis is the most prevalent and severe complication of pregnancy and one of the main causes of maternal and neonatal mortality [6,9]. Unfortunately, the incidence of gestosis notably increased during the recent decade. On the one hand, it was due to unfavorable social factors, such as decrease of population health index, insufficient and irrational nutrition, chronic stress, neglect of medical recommendations [7]. On the other hand, increased incidence of severe gestosis is a medical problem, indicating increased incidence of combined forms, when the clinical picture does not correspond to the true severity of disease, late or inadequate treatment, preterm delivery and progression of gestosis into preeclampsia and eclampsia [3]. Hence, study of the pathogenesis and search for additional diagnostic criteria and prediction of gestosis and its complications [9], specifically evaluation of nonrespiratory functions of the lungs [2] and endothelial lesions, are important trends of research.

MATERIALS AND METHODS

We examined 49 pregnant women with gestosis of different severity with complications, 12 of these with preeclampsia and eclampsia, were examined. Control group consisted of 12 women with normal pregnancy and 16 healthy nonpregnant women. Clinical examinations included evaluation of the clinical status using the APACHE-II score, toxicosis index, hemodynamic, gaseous exchange, hepatorenal function parameters. Anthropometric and clinical parameters of newborns were evaluated. In order to detect the hemostasis-regulating role of the lungs, blood coagulation parameters were measured in mixed venous blood collected through subclavian catheters or from the ulnar vein and in arterial blood collected from the ulnar or radial arteries. The following parameters were evaluated: platelet count (by the method of Fonio), platelet aggregation time with ADP and ristomycin (test for Willebrand factor), blood clotting time (by the method of Lee—White), autocoagulation test (ACT) by the method of E. P. Ivanov, prothrombin index (method of A. J. Quick), fibrinogen content (method of R. A. Rutberg), spontaneous fibrinolysis (method of M. A. Kotovshchikova and B. I. Kuznik), content of soluble fibrin monomer complexes (SFMC, orthophenanthroline tes), heparin resistance of the plasma, and antithrombin-III (AT-III) activity (method of U. Abildgaard) [1,4,5].

The significance of differences was evaluated using nonparametrical Mann—Whitney *U* test and coefficient of correlations was estimated after Spearman.

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0007-4888/01/1326-1187$25.00

RESULTS

All signs of intravascular blood clotting were detected in venous blood of women with normal pregnancy under conditions of physiological shift of hemostasis: hypercoagulation, fibrinogen hyperproduction, markers of disseminated intravascular coagulation (DIC) (paracoagulation products), and compensatory fibrinolysis activation. These shifts were still more pronounced in gestosis (Table 1). However analysis of the arteriovenous difference in normal gestation and initial stages of gestosis showed a corrective role of the lungs: the coagulation potential returned to normal in arterial blood, the levels of fibrinogen and its degradation products decreased, and fibrinolytic activity normalized. The lungs regulated platelet aggregation, which was confirmed by a significant correlation between arteriovenous difference of platelet aggregation time with ADP and the values of this parameter in the blood flowing to the lungs (R=0.69 in normal gestation and R=0.7 in slight and medium severe gestosis, $p<0.05$). In uneventful pregnancy, platelet count and activity of the prothrombin complex factors virtually did not depend on the lungs.

The content of Willebrand factor, a marker of endothelial lesions in gestosis, determines the rate of ristomycin-dependent platelet aggregation. It increased in slight and medium-severe gestosis, this increase being more pronounced in arterial blood. A deficit of AT-III was detected, its degree being closely related to the duration of gestosis. Moreover, the level of this anticoagulant was notably decreased "after the lungs", which indicated its intensive consumption under conditions of intravascular coagulation in the pulmonary circulation.

Progress of gestosis, and development of preeclampsia and eclampsia were paralleled by transformation of chronic DIC into subacute DIC syndrome with augmenting hypercoagulation and hyperaggregation or transition into the hypocoagulation stage. Endothelial lesions augmented, the content of Willebrand factor in the venous blood significantly correlated with the severity of gestosis (R=-0.65, $p<0.02$). Overloading of pulmonary fibrinolytic mechanisms by coagulation and paracoagulation products and their damage in the presence of total endothelial impairment (confirmed by further increase in the level of Willebrand factor in arterial blood) led to exhaustion of the compensatory potential of the lungs.

The regulatory role of the lungs towards aggregation and coagulation activities was no longer detected; critical deviations in these parameters persisted in both venous and arterial blood, no significant arteriovenous difference being detected. A

TABLE 1. Basic Hemostasiological Parameters of Venous/Arterial Blood in Health and Eclampsia ($M\pm m$)

Parameter	Donors (n=16)	Pregnant women	
		healthy (n=12)	with preeclampsia (n=12)
Platelet count, 10^9/liter	249.0±46.8 254.6±44.3	252.6±31.5 256.5±32.4	230.2±21.4 191.5±34.0*°°
Platelet aggregation time with ristomycin, sec	16.2±1.1 15.2±2.2	15.5±1.5 14.5±2.0	9.5±0.5°° 9.0±0.5°°
Blood clotting time, min	7.5±1.4 6.7±0.9	5.5±0.7++ 6.6±1.3	3.6±1.0°° 4.9±0.9°°
Prothrombin index, %	107.0±6.6 107.1±7.8	100.0±7.6 96.6±6.3	101.3±10.2 100.0±6.5
Fibrinogen content, g/liter	2.7±0.2 2.6±0.2	3.8±0.5+ 3.5±0.5++	4.3±0.5 4.2±0.5°°
Spontaneous fibrinolysis, %	20.7±2.6 21.1±3.4	29.4±3.8+ 21±5.5*	13.9±6.0°° 12.9±5.0°°
SFMC content, μg/ml	4.6±0.8 3.5±1.0	16.6±6.0+ 16.5±4.6+	22.0±1.2 23.3±3.1
AT-III activity, %	95.4±9.6 91.4±12.8	87.7±8.3 83.0±7.2	68.2±8.1°° 56.4±13.6*°

Note. *$p<0.05$ for arteriovenous difference; +$p<0.005$, ++$p<0.05$ compared to donors; °$p<0.005$, °°$p<0.05$ compared to healthy pregnant women.

slight, but significant decrease of fibrinogen content after blood passage through the lungs was observed in normal pregnancy, but not in preeclampsia. This was still more manifest in gestosis complicated by respiratory failure: fibrinogen content increased after blood passage through the lungs (from 4.6 to 4.8 g/liter). These changes were paralleled by platelet retention by the lungs, intensive consumption of AT-III, and suppression of fibrinolytic activity "after the lungs".

Clinical examinations of newborns showed a direct relationship between the severity of gestosis, disorders in fibrinolytic mechanisms of the lungs, and the incidence of perinatal diseases. In severe gestosis, perinatal death reached 20%. Analysis of cases with decompensated DIC syndrome manifesting by massive hemorrhages or thrombohemorrhagic complications showed that the severity of hypoxia and metabolic disorders correlated with the severity of blood clotting disorders.

Hence, intravascular blood clotting, detected by laboratory methods in normal pregnancy, does not transform into clinically manifest DIC syndrome due to hemostasis-regulating function of the lungs. In preeclampsia and eclampsia, when the regulatory function of the lungs is inpared, acute DIC syndrome developing due to various causes primarily in the venous flow involves the arterial blood, which leads to development of multiorgan failure. The relationship between the severity of disorders in the hemostasis-regulating function of the lungs and the incidence of fetal hypotrophy and early placenta detachment indicate that exhaustion of the pulmonary compensatory mechanisms impairs microcirculation in the mother—placenta—fetus system. Parallel blood coagulation tests in the venous and arterial blood are useful for the diagnosis and prognosis of gestosis and its complications. The informative tests are presumably evaluation of platelet aggregation time with ristomycin (Willebrand factor), chronometric clotting tests, measurements of fibrinogen and fibrin degradation products, evaluation of spontaneous fibrinolysis and AT-III activity.

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