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LABORATORY MARKERS OF PERINATAL DISORDERS IN WOMEN WITH COVID-19

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Introduction. There is insufficient data in the available literature on the association of laboratory changes in pregnant women with COVID-19, in particular coagulopathy indicators, with adverse pregnancy outcomes.

The aim of the study is to identify potential laboratory markers of perinatal disorders in COVID-19 during pregnancy.

Materials and methods. The comprehensive study included: 200 pregnant women who were hospitalized with COVID-19 during pregnancy (main group) and 50 patients who did not have COVID-19 during pregnancy (control group). The main group was divided into 2 subgroups: O1 – 50 women with adverse perinatal outcomes, O2 – 150 patients with a relatively favorable course of the gestational period. Complete blood count, biochemical indicators, and individual hemostasis parameters were taken into account.

Study results. Potential risk factors for perinatal disorders in COVID-19 include anemia, thrombocytopenia, leukocytosis with increased rod-shaped neutrophils, increased liver transaminases, increased C-reactive protein, increased platelet aggregation, prothrombotic changes in hemostasis, in particular increased D-dimer, endothelial damage (increased von Willebrand factor). High activity of inflammatory processes in pregnant women with COVID-19 underlies systemic vasculitic changes and defects in blood coagulation processes, which cause damage to the maternal-fetal complex.

Conclusions. It is important to monitor blood parameters in pregnant women with COVID-19 for timely detection of deterioration of the woman's condition and possible negative impact on perinatal outcomes.

Keywords: COVID-19, pregnancy, perinatal complications, hemostasis, inflammation.

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ЛАБОРАТОРНІ МАРКЕРИ ПЕРИНАТАЛЬНИХ ПОРУШЕНЬ ЗА НАЯВНОСТІ COVID-19 У ЖІНКИ
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До потенційних факторів ризику перинатальних порушень за наявності COVID-19 можна віднести анемію, тромбоцитопенію, лейкоцитоз із підвищенням палочкоядкрних нейтрофілів, підвищення печінкових трансамфназ, зростання С-реактивного білка, зростання агрегації тромбоцитів, протромботичні зміни гемостазу, зокрема підвищення D-димеру, пошкодження ендотелію (зростання фактора фон Віллебранда). Висока активність запальних процесів у вагітних з COVID-19 лежить в основі системних васкулітних змін і дефектів процесів згортання крові, які обумовлюють пошкодження материнсько-плодового комплексу. У разі COVID-19 у вагітних важливо проводити моніторинг показників крові для своєчасного виявлення погіршення стану жінки й можливого негативного впливу на перинатальні наслідки.

Ключові слова: COVID-19, вагітність, перинатальні ускладнення, гемостаз, запалення.

Introduction. Coronavirus disease 2019 (COVID-19) is a viral respiratory illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The COVID-19 pandemic has posed an unprecedented challenge to healthcare systems worldwide.

COVID-19 can cause thrombotic disease through excessive inflammation, platelet activation, and endothelial dysfunction [1].

Common laboratory abnormalities seen in patients with COVID-19 include lymphopenia [2] and elevated inflammatory markers such as C-reactive protein, D-dimer, ferritin, and interleukin-6 (IL-6) [3], which are associated with a higher risk of requiring mechanical ventilation, intensive care unit admission, or death. IL-6 levels may correlate with disease severity and procoagulant profile [4].

Data related to other tests are less definitive and often contradictory. Disease severity may be associated with prolonged prothrombin time (PT) and increased international normalized ratio (INR) [5], as well as prolonged thrombin time (TT) [6] and a trend

toward reduced activated partial thromboplastin time (APTT) [7].

Taken together, these hemostatic changes suggest a coagulopathy that may predispose to thrombotic events, although the exact cause is unknown. However, it is still unclear whether these hemostatic changes are a specific effect of SARS-CoV-2 or a consequence of a cytokine storm that accelerates the onset of systemic inflammatory syndrome (SIRS), as seen in other viral diseases [8]. Another consideration that has not been explored much is that the hemostatic changes observed in COVID-19 infection are related to liver dysfunction [9].

Pregnancy is a physiological prothrombotic state and therefore there is an increased risk of developing coagulopathy and/or thromboembolic complications associated with COVID-19. During viral outbreaks, pregnant women are at increased risk of respiratory infections due to changes in immune function and adaptive physiological changes such as increased oxygen consumption, upper airway mucosal edema, and diaphragmatic elevation [10, 11].

Physiological changes during pregnancy result in increased D-dimer and fibrinogen levels, as well as decreases in (PT), activated partial thromboplastin time (APTT), and platelet count. In addition to altered coagulation, SARS-CoV-2 infection may lead to additional changes, represented by increased D-dimer levels and prolonged APTT and PTT [12].

Pregnant women have a four- to five-fold higher risk of venous thromboembolism (VTE) than non-pregnant women. In pregnant women with COVID-19, laboratory parameters of hemostasis may coincide with indicators of COVID-19-associated coagulopathy (CAC), disseminated intravascular coagulation (DIC), sepsis-induced coagulopathy (SIC), thrombotic microangiopathy (TMA), and HELLP syndrome [13].

Laboratory studies show that in pregnant women with COVID-19, lymphopenia and elevated C-reactive protein (CRP) are the most frequently reported changes, with a frequency of about 42% and 51%, respectively [14, 15]. Other laboratory abnormalities commonly reported in critically ill patients include elevated neutrophils, thrombocytopenia, liver and kidney function abnormalities, and elevated D-dimer, ferritin, and procalcitonin [16, 17]. Maternal DIC has been reported in association with COVID-19 infection [18]. During pregnancy, COVID-19 coagulopathy in the third trimester has been associated with either clinical manifestations that mimic normotensive HELLP syndrome, associated with thrombocytopenia and elevated liver enzymes [19], or hyperfibrinolytic coagulopathy with bleeding [20].

There is limited evidence in the available literature to investigate the association of laboratory abnormalities in pregnant women with COVID-19, particularly coagulopathy indices, with adverse pregnancy outcomes. It is worth noting only a recent study of the role of hemostasis system parameters in the assessment of preeclampsia of varying severity and their relationship with pregnancy outcomes, which included 168 patients with PE who were hospitalized in a hospital in the Chinese province of Yunnan [21].

The aim of the study is to identify potential laboratory markers of perinatal disorders in COVID-19 during pregnancy.

Materials and methods. The comprehensive study included 250 pregnant women: the main group – 200 women who were hospitalized with COVID-19 during pregnancy and the control group – 50 patients who did not suffer from COVID-19 or other acute respiratory viral diseases during pregnancy. To determine the risk factors for adverse perinatal outcomes in women with COVID-19, the main group was divided into 2 parts: subgroup O1 – 50 women with adverse perinatal outcomes (fetal distress, fetal growth retardation, premature birth, severe neonatal asphyxia, perinatal death), subgroup O2 – 150 patients with a relatively favorable course of the gestational period).

A comprehensive blood test was performed on an automatic hematology machine Mindray BC-3200 by photometric and conductometric methods with venous blood samples using reagents from the manufacturer “Mindray”. Biochemical blood parameters were studied on a biochemical analyzer Mindray BA-88A with reagents from the manufacturer “Mindray” with venous blood plasma samples. The study of hemostasis system parameters was carried out using screening coagulation tests on a semi-automatic coagulometer Helena C-2.

Statistical processing of primary data was carried out using the standard Microsoft Office Excel 2010 package and the STATISTICA 6.0 software package.

Research results and their discussion. The average values of the comprehensive blood test indicators of pregnant women with COVID-19 did not differ statistically from those of pregnant women in the control group (Table 1), however, certain changes can be noted with a more detailed analysis of the distribution of indicators in the groups. Anemia was detected in 46.0% of pregnant women in the main group versus 16.0% ($p < 0.05$) in women in the control group, and in the control group only mild anemia was noted, and in women with COVID-19, moderate anemia was recorded in 21.0% and severe anemia in 7.0%. In group O1, the frequency of anemia was more than 2 times higher than in group O2 (82.0% versus 34.0%, respectively, $p < 0.05$), and moderate anemia prevailed in the structure by severity (26.0% versus 10.7%, $p < 0.05$), and severe anemia was recorded in 16.0% of patients (versus 4.0% in subgroup O2, $p < 0.05$).

In the main group, changes in the number of leukocytes were noted: leukopenia characteristic of the onset of the disease in some patients at the time of hospitalization was replaced by leukocytosis in some patients, more pronounced in pregnant women of group O1 (32.0% versus 14.7% in group O2, $p < 0.05$). Certain changes in the blood formula were also noted. When a bacterial infection was added, a shift to the left of the leukocyte formula (an increase in the content of rod-shaped leukocytes) was observed in 36 (72.0%) and 68 (45.3%) pregnant women of groups O1 and O2 ($p < 0.05$).

Analysis of biochemical blood parameters revealed changes characteristic of pregnant women with COVID-19 (Table 2). A significant increase in transaminase levels was noted both in relation to the indicators of women in the control group and in patients in the group with perinatal losses in relation to the control and group O2. Alanine aminotransferase (ALT) was above the normative values in 110 (55.0%) women in the main group, of which

Table 1

Indicators of a comprehensive blood test for COVID-19 in pregnant women

Indicator	Main group, n = 200	Group O1, n = 50	Group O2, n = 150	Control, n = 50
Hemoglobin, g/L	96.5 ± 6.41	94.5 ± 7.6	99.7 ± 5.6	108.3 ± 7.1
Erythrocytes, $x10^{12}$/ L	3.6 ± 0.8	3.5 ± 0.5	3.8 ± 0.7	3.9 ± 0.4
Platelets, 10^9/ L	210.7 ± 20.5	180.2 ± 17.2*	215.3 ± 19.1	234.5 ± 14.2
Hematocrit, %	36.7 ± 4.2	30.5 ± 2.6*	38.3 ± 4.1	41.3 ± 4.4
Leukocytes,10^9/ L	12.8 ± 1.8	15.1 ± 1.4*#	10.1 ± 0.7	9.7 ± 0.8
lymphocytes, %	24.7 ± 3.1	20.9 ± 2.6*	27.3 ± 2.1	29.3 ± 2.8
monocytes, %	5.2 ± 0.8	5.7 ± 1.3	5.3 ± 0.7	4.6 ± 0.7
eosinophils, %	1.8 ± 0.6	1.6 ± 0.5	1.9 ± 0.4	2.1 ± 0.4
rod neutrophils, %	5.6 ± 1.4	7.6±1.6*	4.6 ± 1.5	2.9 ± 1.4
segmented neutrophils, %	58.2±6.0	62.5±5.8	56.4 ± 4.0	55.3 ± 4.5

Notes: * – the difference is significant compared to the indicator of women in the control group ($p < 0.05$).

– the difference is significant compared to the indicator of women in the O2 group ($p < 0.05$).

Table 2

Blood biochemistry parameters in COVID-19 in pregnant women

Indicator	Main group, n = 200	Group O1, n = 50	Group O2, n = 150	Control, n = 50
AST, U/L	36.8 ± 7.7*	45.4 ± 7.3*#	28.1 ± 6.9	21.5 ± 5.2
ALT, U/L	39.3 ± 8.1*	47.6 ± 6.4*#	27.3 ± 7.2	24.6 ± 6.5
Total bilirubin, μmol/L	12.7 ± 3.4	15.4 ± 4.2	10.6 ± 5.1	11.5 ± 3.7
Urea, μmol/L	2.8 ± 0.98	3.5 ± 0.58	2.7 ± 0.74	2.6 ± 0.72
Creatinine, μmol/L	71.9 ± 6.1	75.3 ± 7.1*	66.2 ± 6.5	54.8 ± 7.5
C-reactive protein, g/L	14.8 ± 4.4*	18.3 ± 5.1*	8.3 ± 4.7	4.5 ± 3.1

Notes: * – the difference is significant compared to the indicator of women in the control group ($p < 0.05$).

– the difference is significant compared to the indicator of women in the O2 group ($p < 0.05$).

42 (84.0%) patients in group O1 and 68 (45.3%) in group O2 ($p < 0.05$). The level of aspartate aminotransferase (AST) was also significantly increased: above the norm in 40 (80.0%) patients in group O1 and in 66 (44.0%) in group O2 ($p < 0.05$).

No differences were found between the groups in terms of total bilirubin and urea. The creatinine level was significantly increased only in group O1 relative to the control due to an increase in some cases. The level of the inflammatory marker CRP was significantly increased in the main group compared to the control group, and in group O1 its value was significantly higher compared to group O2 (18.3 ± 5.1 versus 8.3 ± 4.7 g/l, $p < 0.05$).

Analysis of hemostasis system indicators revealed a prothrombotic orientation of changes in COVID-19 in pregnant women (Table 3). Against the background of relative thrombocytopenia, an increase in ATA-induced platelet aggregation is observed (65.6 ± 4.8% versus 50.2 ± 5.8% in groups O1 and O2, $p < 0.05$). The prothrombotic orientation of changes in the hemostasis system corresponds to a slight increase in fibrinogen content and an increase in the prothrombin index, a relative decrease in activated partial thromboplastin time (APTT).

The most pronounced changes in COVID-1 in pregnant women were noted for D-dimer (271.1 ± 19.6 ng/ml in the main group versus 196.2 ± 22.7 ng/ml in women in

Table 3

Indicators of the hemostasis system in COVID-19 in pregnant women

Indicator	Main group, n = 200	Group O1, n = 50	Group O2, n = 150	Control, n = 50
ATA-induced platelet aggregation index, %	57.5 ± 5.7	65.6 ± 4.8*#	50.2 ± 5.8	47.6 ± 4.3
Fibrinogen, g/l	4.2 ± 0.9	4.5 ± 0.8	4.1 ± 0.9	3.1 ± 0.8
Prothrombin index, %	112.9 ± 8.3	120.4 ± 11.5*	107.9 ± 9.1	92.5 ± 7.8
APTT, s	30.2 ± 3.1	27.5 ± 3.1	31.1 ± 2.8	36.3 ± 2.6
INR	0.82 ± 0.07	0.79 ± 0.07	0.86 ± 0.08	0.97 ± 0.06
D-dimer, ng/ml	271.1 ± 19.6*	321.6 ± 21.3*#	242.1 ± 20.5	196.2 ± 22.7
Von Willebrand factor (VWF:AG), IU/ml	1.43 ± 0.14*	1.68 ± 0.12*	1.35 ± 0.19*	0.78 ± 0.11

Notes: * – the difference is significant compared to the indicator of women in the control group ($p < 0.05$).

– the difference is significant compared to the indicator of women in the O2 group ($p < 0.05$).

the control group, $p < 0.05$), the highest values (in three patients more than 10,000 ng/ml) were recorded in group O1 (average level 321.6 ± 21.3 versus 242.1 ± 20.5 ng/ml in patients in group O2, $p < 0.05$). In general, an increase in the indicator was observed in 42 (84.0%) pregnant women in group O1 and in 93 (62.0%) in group O2 ($p < 0.05$). The violation of endothelial function in COVID-19 is evidenced by an increase in the level of von Willebrand factor as determined by its antigen (VWF:AG) to 1.43 ± 0.14 versus 0.78 ± 0.11 IU/ml in women of the main group compared to the control group, $p < 0.05$).

Conclusions. Potential risk factors for perinatal disorders in COVID-19 include anemia, thrombocytopenia, leukocytosis with an increase in rod-shaped neutrophils, an increase in hepatic transaminases, an increase in C-reactive protein, an increase in platelet aggregation, prothrombotic changes in hemostasis, in particular an increase in D-dimer, endothelial damage (an increase in von Willebrand factor).

High activity of inflammatory processes in pregnant women with COVID-19 underlies systemic vasculitic changes and defects in blood coagulation processes, which cause damage to the maternal-fetal complex.

With COVID-19 in pregnant women, it is important to monitor blood parameters for timely detection of deterioration of the woman's condition and possible negative impact on perinatal outcomes.

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