IMMUNOHISTOCHEMICAL ASSESSMENT OF EPIDERMAL GROWTH FACTOR RECEPTOR AND PROHIBITIN EXPRESSION IN "POST-COVID" PLACENTAS: RESULTS OF A COMPARATIVE CROSS-SECTIONAL STUDY

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INTRODUCTION

The pandemic caused by the COVID-19 infection, since its aggravation in 2019, continues to be the subject of attention of researchers due to the mutation of the virus and the high contagiousness, morbidity and mortality [1]. The impact of the SARS-CoV-2 virus on the course of pregnancy and perinatal outcomes, issues of transplacental infection of newborns are also in the area of constant interest. Assessment of the anatomical, functional, metabolic, barrier and other functions of the placenta is an important area of these studies. Particular attention in protecting the intrauterine fetus is paid to the role of the placental barrier, which is based on the special structure of the multinucleated syncytiotrophoblast in the feto-maternal interface area, where key functions of the placenta are realized, incl. secretion of immune and endocrine factors, gas exchange, protection against pathogens, etc. [2].

Early studies on the pathology of the placenta against the background of maternal illness COVID-19 showed mixed results, including as well the absence of a characteristic histopathological picture in "post-COVID" placentas [3], although it is assumed that the placenta is involved in the inflammatory process with the development of preeclampsia, intrauterine growth restriction, miscarriage and perinatal losses [4–6]. There is also information about a high risk of respiratory disorders in children whose mothers had COVID-19 during pregnancy [7, 8].

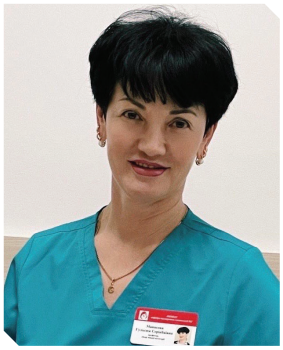
The histopathological features of the placenta during COVID-19 infection continue to be studied and, according to a number of studies, the most common manifestations include trophoblast necrosis, histiocytic intervillositis, intervillous fibrin deposition, etc. [9–11].

The widespread use of proteomic research methods currently allows for a deeper approach to explaining the pathogenesis of diseases and the formation of targeted ways for their prevention and treatment. The study of the human placental proteome also turned out to be in the field of these interests, in particular, this concerns multifunctional proteins – epidermal growth factor (EGF) and prohibitin (PHB).

The zone of EGF activity includes proliferation and differentiation of trophoblast cells, angiogenesis and placental growth: changes in its synthesis are observed in some complications of pregnancy, in particular in preeclampsia. EGF has been suggested to act as an autocrine factor in regulating early placental growth [12]. There are studies showing that exogenous administration of EGF protects against apoptosis induced by cytokines and reactive oxygen species and this may be an effective way to improve placental function [13, 14].

Another placental protein, prohibitin, also plays a role in the proliferation and migration of placental vascular endothelial cells and there is information about its possible participation in the genesis of recurrent miscarriage [5, 15]. Pleiotropic effects of PHB are mediated in a cell- and tissue-specific manner, associated with cell differentiation, growth and metabolism. PHB participates in mitochondria-mediated antiviral innate immunity, promotes pulmonary vascular remodeling; its overexpression is aimed at preserving mitochondrial respiration and mitochondrial structure [16, 17]. PHB also has a neuroprotective effect, which is mediated by nitric oxide (NO), which increases the resistance of neurons to ischemia-reperfusion injury under stress [18]. The results of recent research allow us to speak of PHB as a new biomarker and molecular target for therapeutic intervention in cardiovascular, neurodegenerative and other metabolic diseases [19].

The COVID-19 pandemic was an unconditional trigger for the intensification of scientific research and the study of the role of some mediators of intercellular interaction in the pathogenesis of the disease, including EGF and PHB were no exception. Thus, it has been established that the SARS-CoV-2 spike glycoprotein activates EGF receptors (EGFR) and its downstream signaling pathway in vitro [20]. EGFR, along with angiotensin I converting enzyme 2, serves as a coreceptor of the epidermal growth factor receptor / mitogen signaling pathway – activated protein kinase (EGFR/MAPK) and promotes SARS-CoV-2 infection [21]. A correlation has



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been identified between the severity of COVID-19, the severity of pulmonary fibrosis and EGFR expression [22, 23].

Regarding PHB, it has been established that the second non-structural protein of the SARS-CoV-2 polyprotein (NSP2) binds to prohibitin 1 and 2 (PHB1 and PHB2) and this may contribute to disruption of the host cell relationship and environment. It is possible that the effect on PHB and disruption of the PHB/NSP2 complex may be a target for resolving the issue of virus penetration into cells [24–26].

Thus, the information provided was the rationale for the **objective of the study**: to analyzed of the perinatal outcomes of pregnancy and to study an immunohistochemical (IHC) assessment of the expression of EGFR and PHB in the placenta of women who had COVID-19 during pregnancy and compare the data with their expression in the placentas of healthy women.

MATERIALS AND METHODS

Population

A total of 98 women were included in the study:

- the main group included 58 women who had COVID-19 during pregnancy;
- 40 apparently healthy women made up the control group.

The study was carried out at the hospital base of Odessa and the Odessa region for the provision of medical care to pregnant women and women in labor with a verified diagnosis of COVID-19 – "Maternity Hospital No. 2" of the Odessa City Council for the period from November 1, 2021 to December 31, 2022.

Criteria for inclusion in the main group: diagnosis of COVID-19, verified by detecting SARS-CoV-2 virus RNA using real-time polymerase chain reaction in biomaterial from the back wall of the pharynx and nose in a certified laboratory (biomaterial was collected for research, transportation was carried out according to the requirements of regulatory documents of the Ministry of Health of Ukraine). These were pregnant women with moderate severity of the disease (women with severe forms were hospitalized in a multidisciplinary institution of the 3rd level of medical care). The control group included women without COVID-19 infection during this pregnancy. There were no women with severe extragenital pathology (chronic arterial hypertension, severe diabetes mellitus, etc.) in both groups. No infections were detected in these women during the gestational period. Clinical data on the course of pregnancy, pregnancy outcomes for the mother and fetus, and laboratory data were analyzed.

Ethical aspects of the study

The study was approved by the Ethical Commission of the Odessa National Medical University (protocol No. 17 of 19 November 2021) and was carried out in accordance with the guidelines of the Declaration of Helsinki. All patients gave informed consent to participate in the study upon admission to the hospital.

This work is a part of the scientific theme of the Department of Obstetrics and Gynecology of the Odessa National Medical University "The latest therapeutic, diagnostic and preventive approaches to diseases of the female reproductive system and high-risk pregnancy" (registration number No. 0117 U007494).

Study of placentas

After birth, placentas were fixed in a 10% buffered formalin solution for 48 hours and transported to the Odessa Regional Pathoanatomical Bureau, where the study was carried out by a perinatal pathologist who was aware of the "COVID status" of the biomaterial. Morphological examination of placentas was carried out taking into account the requirements of regulatory documents of the Ministry of Health of Ukraine. The recommendations of the Amsterdam Placental Workshop Group Consensus Statement (2016) were used to describe the histopathological changes in placentas [27], 8 samples of placental tissue from each placenta were taken for microscopic examination after macroscopic assessment and morphometry of the placenta – pieces measuring 1 × 1 cm in 2 sections from the central, paracentral and marginal section of the placenta, 1 strip of membranes 8 cm long, 1 piece of umbilical cord. The material was fixed in a 10% formaldehyde solution, dehydrated in 4 alcohol solutions of various concentrations, 2 chloroform solutions of various concentrations, then in 2 containers of paraffin with base wax. Sections 5 μm thick (using a sled microtome) were stained with hematoxylin and eosin and covered with polystyrene. Microscopic evaluation (magnifications 10 × 10, 10 × 20 and 10 × 40) was carried out using a Leica DMIS microscope No. 760.

IHC study was carried out for 25 placentas from the main group and 20 placentas from the control group (blind selection). For this purpose, the material (sections 4 μm thick) were placed on charged glasses (Superfrost Plus / Plus Gold / Polysine glasses with an adhesive coating), dried at a temperature of 60 °C (for 12–14 hours), then deparaffinized and rehydrated, followed by thermally induced epitope extraction. The tissue was boiled in a Pt module using Vitro S.A. buffer with ethylenediaminetetraacetic acid (EDTA) pH 84 for 20 minutes at 95 °C. The glass was then washed 3–5 times in distilled water and cooled at room temperature for 20 minutes. Blocking of endogenous peroxidase was carried out in for 10 minutes at room temperature using peroxidase solution (code MAD-021540Q-125).

To determine a mitochondrial marker PHB incubation was carried out for 10 minutes with primary monoclonal antibodies specific to PHB – mouse monoclonal antibody against human PHB (clone mtc02) at a dilution of 1:50 (model MAD-007018q, Sevilla, Spain). To detect the EGFR, incubation was carried out for 20 minutes with purified rabbit monoclonal antibodies against human EGFR – clone EP223 at a dilution of 1:50 (model MAD-000664Q, Vitro Master Diagnostica, Spain).

Visualization of the results was carried out using the Master Polymer Plus system (including 3,3'-diaminobenzidine; MAD-000237QK); counterstaining was performed with modified hematoxylin. The entire immunohistochemical procedure was carried out using a Thermo Fisher Scientific RT module system (PT 12004W1204 2012, USA) complete with an autostainer for automation of IHC staining with preliminary probolide preparation. A rotary microtome Leica RT 2125 (9409/05.2006), histoplate Leica Biosystems HI 1210 (No. 6668/02/06, Germany) were also used at the study. Microscopic assessment was carried out using a Granum microscope No. 3302/2002 14382 (Ukraine), Euromex CEPII I Scope (Netherlands) and images were acquired and analyzed using Lucia G 4.7 software [28].

Statistical tests

Considering the nature of the data obtained from the IHC study, we used the transformation of qualitative indicators for the mathematical assessment of the data – categorical variables (IHC microscopy, where the expression of receptors (PHB and EGFR) was assessed from their absence (–) to presence (+++) into quantitative ones (from 0 up to 3). For statistical analysis the was used Kolmogorov-Smirnov test to determine the normality of distribution, the non-parametric Mann-Whitney test (U_{emp}) to compare the expression of PHB and EGFR in placentas and other indicators, the Kruskal-Wallis test (a non-parametric alternative to the one-way ANOVA test for independent indicators), calculation of Fisher's exact test and χ^2 test, calculation of relative risk (RR) and odds ratio (OR), 95% confidence interval (CI). A statistically significant p value was defined as a value less than 0.05. Statistical tests were performed on the online platform Social Science Statistics [29].

RESULTS

All participants belonged to Slavic nationality; there were no significant differences between the groups based on age and anthropometric data. There were more city residents in both groups than rural ones (65.51% vs 80% in the main and control groups); however, living in rural areas (34.45% vs 20%) increases the risk of COVID-19 incidence (OR = 2.105, 95% CI 0.818–5.418). By the nature of the profession (mental work, physical work, housewives), no significant differences were found in the groups (χ^2 = 1.3676, p = 0.504703, p > 0.05) (Table 1). Noteworthy is the higher body mass index in the group with COVID-19 (27.32 ± 4.48 vs 22.8 ± 2.30 kg/m^2; p = 0.000023).

A statistically significant difference in the rate of preterm birth between the groups was revealed: the risk of preterm birth in the COVID group is almost 5 times higher than in the control group (F = 0.039, p < 0.05, RR = 4.14, OR = 4.96, 95% CI 1.044–23.526). The frequency of cesarean sections is

Table 1. Demographic and clinical features of the participants

Indicators	Main group, n = 58	Control group, n = 40	Reliability, p < 0.05
Mental labour, n (calculated quantity) [criterion X^2]	32 (31.37) [0.01]	21 (21.63) [0.02]	χ^2 = 1.3676, p = 0.504703, p > 0.05
Physical labour, n (calculated quantity) [criterion X^2]	8 (10.06) [0.42]	9 (6.94) [0.61]	
Housewives, n (calculated quantity) [criterion X^2]	18 (16.57) [0.12]	10 (11.43) [0.18]	
Age, M ± m, years	29.21 ± 4.3	30.35 ± 3.12	t = 0.21, p = 0.830553
Average weigh, M ± m, kg	74.6 ± 13.82	63.18 ± 7.13	t = 0.79, p = 0.429550, p > 0.05
Height, M ± m, sm	167.27 ± 5.33	168.65 ± 5.63	t = 0.17, p = 0.464535, p > 0.05
Body mass index, M ± SD, kg/m^2	27.32 ± 4.48	22.8 ± 2.30	F = 19.77899. p = 0.000023.
Primapara, n (%)	39 (67.24)	22 (55.00)	F = 0.2895; p > 0.05
Multiparous, n (%)	19 (32.76)	18 (45)	
Partus matures, n (%)	46 (79.3)	38 (92.5)	F = 0.039 p < 0.05 OR = 4.957, 95% CI = 1.044–23.526
Preterm birth + late abortions, n (%)	12 (20.68)	2 (5)	
Cesarean section, minor, n (%)	1 (1.72)	0	-
Preterm birth, n (%)	9 (15.51)	2 (5)	F = 0.1911 p > 0.05 OR = 3.490, 95% CI = 0.712–17.108
Birth *per vias naturalis*, n (%)	47 (81.03)	35 (87.5)	F = 0,5792 p > 0.05 OR = 1.638, 95% CI = 0.522–5.144
Cesarean section, n (%)	11 (34.4)	5 (12.5)	
Vacuum extraction of the fetus, n (%)	2 (3.57)	0	F = 0.5119; p > 0,05
Manual separation of the placenta, n (%)	2 (3.57)	0	F = 0.5119 p > 0.05

also higher in women of the main group (OR = 1.638, 95% CI 0.522–5.144). Indications for abdominal birth in patients in the main group were obstructive labor (labor anomalies – 37.5%, clinically narrow pelvis – 4.17%, cervical dystocia – 4.17%), fetal distress – 29.17%, abruption a normally located placenta – 8.34%, the use of assisted reproductive technologies in combination with women's refusal to give birth *per vias naturalis* – 12.48%, the presence of a scar on the uterus after a previous cesarean section – 4.17%. In the main group, in contrast to the control group, surgical aids were used in the 2nd stage of labor (2 cases each of vacuum extraction of the fetus and manual separation and release of the placenta), but the sample size does not allow us to talk about statistical significance ($F = 0.5119$, $p > 0.05$).

Most of the women from the main group fell ill in the 3rd trimester of pregnancy – 65.51% (38 persons), in the 2nd trimester – 25.86% (15 persons), in the 1st trimester only 8.62% (5 persons) (Fig. 1).

In the main group 55 live children were born (3 late abortions with fetal weights up to 500 g, 1 of them was a minor caesarean section due to premature placental abruption). Analysis of the newborns' condition at 1 minute after birth in the study groups revealed a statistical difference between the groups in terms of the Apgar scale (M ± SD: 6.48 ± 2.39 vs 8.05 ± 0.54 points; $\chi^2 = 21.933$ (df = 4), $p < 0.00$). 6 children (10.34%) required intensive care, 3 (5.17%) needed pulmonary surfactant administration due to respiratory problems, and there was 1 case of a stillbirth. There were no perinatal losses in the control group (Table 2).

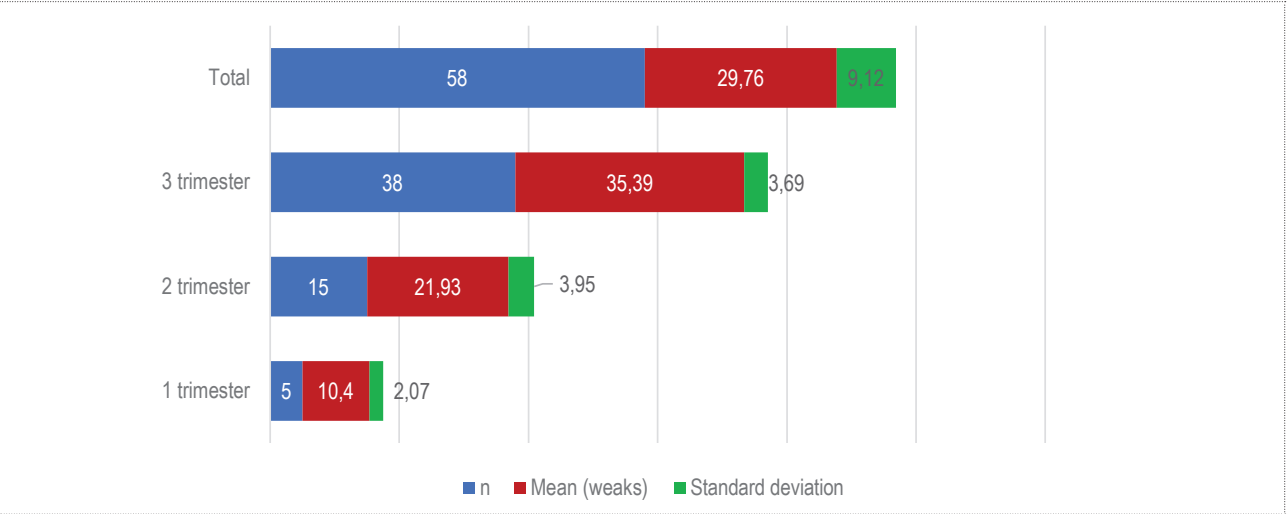


Figure 1. The gestational age at the time of the COVID-19 disease:
the average period of morbidity was 29.6 ± 9.1 weeks. The difference in the frequency of morbidity depending on the gestational age was significant for each trimester ($F = 148.38358$, $p < 0.00001$).

Table 2. Anthropometric characteristics and status of newborns in women who have recovered from COVID-19 and in healthy pregnant women

Indexes \ Groups	Main group, n = 55	Control group, n = 40	p
Weigh, M ± SD, g	3067.93 ± 620.21	3617.25 ± 354.58	t = 5.81, p = 0.00000 A = 27.76675, p < 0.00001
Height, M ± SD, sm	50.4 ± 2.91	54.25 ± 2.08	t = 6.92, p = 0.00000 F = 40.36303, p < 0.00001
Apgar score, n (%)			
< 6	3 (5.17)	0	$\chi^2 = 21.933$ df = 4 p < 0.001
6	1 (1.72)	0	
7	24(41.37)	8 (20)	
8	26 (44.82)	21 (52.5)	
9	0	11 (18.96)	
Still birth, n (%)	1 (1.72)	0	F = 1, p > 0.05
Features of management			
Need an intensive care unit, n (%)	6 (10.34)	0	F = 0.0784, p > 0.05
Surfactant administration, n (%)	3 (5.17)	0	F = 0.2678, p > 0.05
Artificial respiration / continuous positive airway pressure, n (%)	1 (1.72)	0	F = 1, p > 0.05

The average weight (3067.93 ± 620.21 vs 3617.25 ± 354.58 g, p < 0.00001) and height (50.4 ± 2.91 54.25 ± 2.08 cm, (p < 0.00001)) of newborns in the group of pregnant women who had recovered from COVID-19 were significantly less than in healthy pregnant women. The minimum weight of a newborn in the main group was 810 g, the maximum was 4400 g.

Data from macroscopic and microscopic assessment of placentas in groups, certain features of the histological structure of the placenta regarding both maternal and fetal vascular malperfusion are presented in the Table 3.

Hemodynamic disturbances: congestion of the villous vessels (26 – main group), haemorrhage in the intervillous space (18 – main group), haemorrhage in the basal lamina (11 – main group, 1 – control group), haemorrhage in the fetal membranes (19 – main group, 4 – control group) (p < 0.05).

The placentas did not differ in weight or location of the umbilical cord root between the groups. A significant difference was revealed in the frequency of necrotic changes in the trophoblast (internal maternal infarctions of the placenta – 53.45% vs 12.5%; agglutination of the villi with the formation of a significant number of syncytial nodules – 79.3% vs 15%). The following histological patterns were also found: intervillous thrombosis (20.69% vs 5%), deposition of perivillous fibrin (20.69% vs 12.5%), chorangiosis (24.14% vs 51%). Data for the inflammato-

Table 3. Macro- and microscopic characteristics of placentas in groups

Variable		Main group, n = 58	Control group, n = 40	p
Macroscopic features of placentas				
Placental weight M ± σ, g		433.79 ± 106.12	493.32 ± 74.07	t = 0.46, p = 0.646568
Cordincertion				
Central, n (%)		15 (25.6)	9 (22.5)	F = 0.81281, p > 0.05
Eccentric, n (%)		40 (68.9)	29 (72.5)	F = 0.82286, p > 0.05
Marginal, n (%)		3 (5.17)	2 (5)	F = 1, p > 0.05
Hypercoil, n (%)		8 (13.79)	6 (15)	F = 1, p > 0.05
Lack of Wharton's jelly, n (%)		10 (17.24)	3 (7.5)	F = 0.22901
Histopathological characteristics of placentas, n (%)				
MVM	Infarctions of the placenta (villous)	31 (53.45)	5 (12.5)	χ^2 (1, N = 98) = 6,50, p = 0.010735, OR = 8.037, 95% CI 2.758-23.423
	Villous agglutination with an increase in the number of syncytial nodules	46 (79.3)	6 (15%)	F = 0.00001, RR = 1.94, OR = 21.722, 95% CI 7.409–63.684
FVM	Avascular / hypovascular villi	5 (8.62)	0	F = 0.0097, p < 0.05
	Chorangiosis (compensatory villous angiomatosis)	14 (24.14)	6 (15)	F = 0.3164 χ^2 (1, n = 98) = 1.217; p = 0.269953
AIP	Serous basal deciduitis	12 (20.69)	4 (10)	F = 0.1789, RR = 2.07, OR = 2.35, 95% CI 0.698–7.895
CIP	Lymphoid infiltration	10 (17.24)	5 (12.5)	F = 0.5807, RR =1.35, OR = 1.46, 95% CI 0.591–4.645
OTHER	Hemodynamic disorders	31 (53.45)	6 (15)	F = 0.0001
	Intervillous thrombosis	12 (20.69)	2 (5)	F = 0.41692, p > 0.05 OR = 1.826, 95% CI 0.589–5.665
	Deposition of perivillous fibrin	12 (20.69)	5 (12.5)	F = 0.4169
	Haemorrhage in Wharton's jelly	12 (20.69)	1 (2.5)	F = 0.0129
	Calcium salt deposition	18 (31.03)	10 (25)	F= 0.65, p > 0.05 OR = 1.35 95% CI 0.545–3.342

AIP – acute inflammatory process; CIP – chronic inflammatory process; MVM – maternal vascular malperfusion: FVM – fetal maternal vascular malperfusion; OTHER – other pathological patterns of the placenta.

ry process in the form of lymphoid infiltration of the basal plate were found in 25.86% of "post-COVID" placentas, serous basal deciduitis – in 20.69%. Noteworthy is the high frequency of hemodynamic disorders in "post-COVID" placentas (F = 0.0001) in the form of congestion of the vessels of the chorionic plate and sclerotic changes in the terminal chorionic villi, hemorrhages in the intervillous subchorionic space (31.03%), in the fetal membranes (32.75%), in the decidua and basal plates (18.96% each)

Results of immunophenotyping of placentas

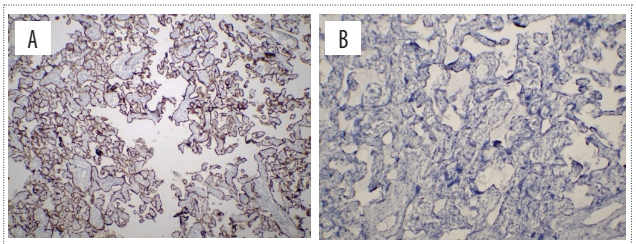
The results of the estimation of EGFR and PHB expression in the groups were characterized by an abnormal distribution (EGFR – K-Stest: 54087 vs 46815, p = 0.00015; PHB – K-Stest: 18874 vs 47948, p = 0.00009). Immunophenotyping of placentas showed a positive EGFR expression status in the compared groups (from (+) to (+++) and there were no differences in the degree of expression between groups (U_{emp} = 197.5, z = 1.18776, p = 0.23404), while the degree of expression of the mitochondrial marker PHB was significantly greater in post-COVID group (U_{emp} = 87.5, z = 3.63182, p = 0.00028) (Table 4).

Table 4. Results of immunophenotyping of placentas for the expression of EGFR and PHB in "post-COVID" placentas and placentas of healthy women

Indexes	EGFR	PHB
Main group, n = 25	2.96 ± 0.2	1.52 ± 1.12
Control group, n = 20	2.75 ± 0.44	0.25 ± 0.5
p	U_{emp} = 197.5, z = 1.18776, p = 0.23404	U_{emp} = 87.5, z = 3.63182, p = 0.00028

Note: Categorical variables obtained from microscopic evaluation of IHC results were converted into quantitative ones: the expression of PHB and EGFR receptors was assessed from their absence (–), which corresponded to 0, to presence (maximum +++), which corresponded to 1, 2 and 3 (p < 0.05).

The results of microscopic evaluation with expression variants of EGFR (EP22)) and PHB (MTC02) in the control group are presented at Figures 2–5 (histology/immunohistochemistry (H/IHC)).



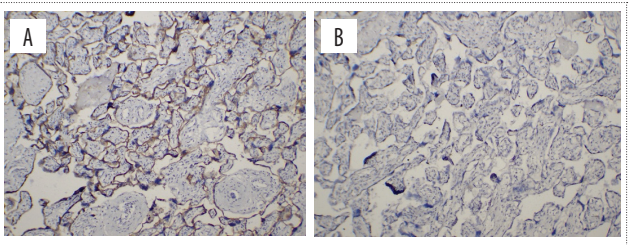
A. №129–32(1) × 200.jpg
Status EGFR (+++)

B. №129–32(2) × 400.jpg.
Status PHB (–)

Figure 2. H/IHC No. 129 – 32; mature placenta with a positive status of EGFR and a negative status of PHB receptors:
A – EGFR status (+++); B – PHB status (–)

The results of microscopic evaluation with expression variants of EGFR (EP22) and PHB (MTC02) in the COVID-19 group are presented at Figures 6–10 (H/IHC).

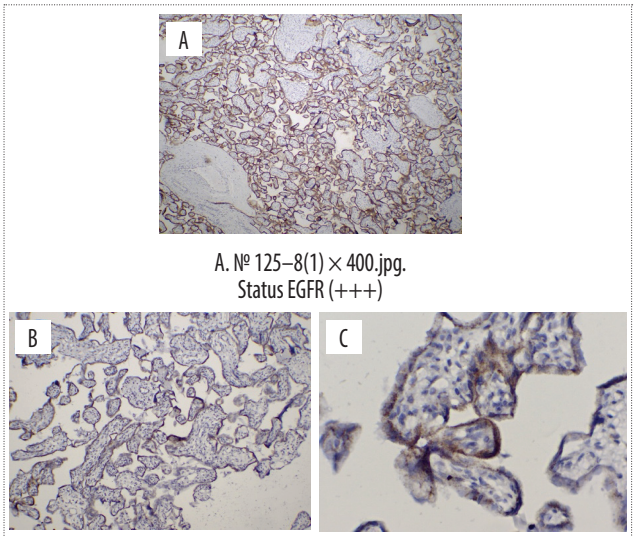
As noted, EGFR expression in placentas did not differ between groups; in addition to this fact, a one-way Kruskal-Wallis analysis of variance found that it does not depend on the COVID history (H = 1.438 (1, n = 45), p = 0.23046, RR = 1, OR = NaN (Not-a-Number), 95% CI 0.0113–0.4087), while PHB expression is significantly associated with the incidence of COVID-19 (H = 12.2933 (1, n = 45). P =0.00045, RR = 3.04, OR = 9.5, 95% CI 2.423–37.249).



A.№ 145–48(1) × 400.jpg.
Status EGFR(EP22) (++)

B. № 145–48(2) × 400.jpg.
Status PHB (MTC02) (–)

Figure 3. H/IHC No. 145–48; mature placenta with a positive status of EGFR and a negative status of PHB receptors:
A – EGFR status (++); B – PHB status (–)



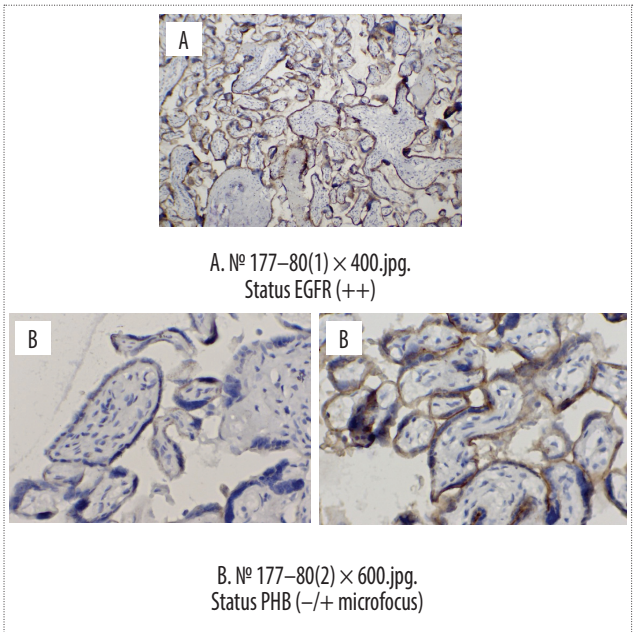
A. № 125–8(1) × 400.jpg.
Status EGFR (+++)

№ 125–8(2) × 400.jpg.

№ 125–8(2) × 600.jpg

B. Status (–/++) microfocus

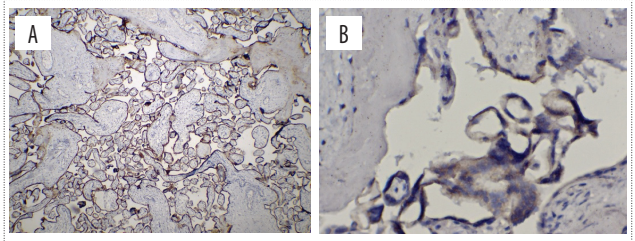
Fig. 4. H/IHC No. 125–8: pathologically immature placenta, a variant of dissociated maturation of the chorion, with a positive status of EGFR and PHB receptors.
A – EGFR status (+++); B – RNV status (–/++)



A. № 177–80(1) × 400.jpg.
Status EGFR (++)

B. № 177–80(2) × 600.jpg.
Status PHB (–/+ microfocus)

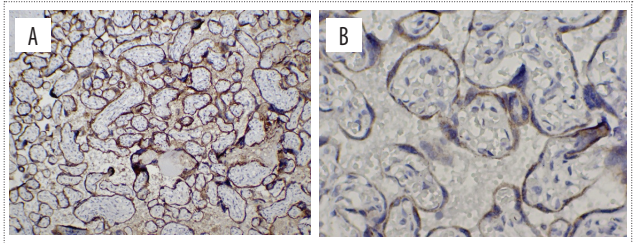
Figure 5. H/IHC No. 177–80: pathologically immature placenta, a variant of dissociated chorion maturation, with a positive status of EGFR and PHB receptors.
A – EGFR (EP22) status (++); B – PHB status (–/+)



A. № 18121–24(1) × 200.jpg. Status EGFR (+++)

B. № 18121–24(2) × 600.jpg. Status PHB from + to ++

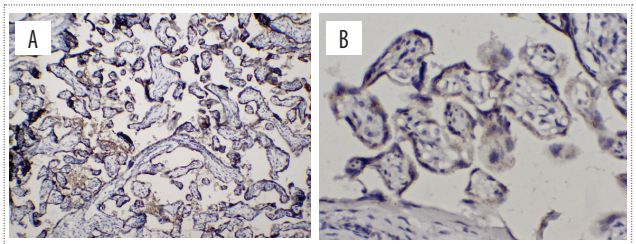
Figure 6. H/IHC No. 117–80. Pathologically immature placenta, a variant of dissociated maturation of the chorion, with a positive status of EGFR and PHB receptors,
A – EGFR (EP22) status (+++); B –PHB status (–/++)



A. № 27525–28 (1) × 400.jpg. Status EGFR (+++)

B. № 27525–28(2) × 600.jpg. Status PHB (+++)

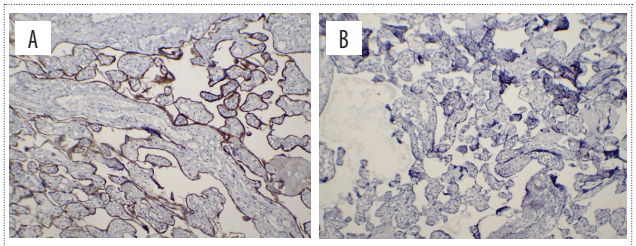
Figure 7. H/IHC No. 27525–28: mature placenta with a positive status of EGFR and PHB,
A –EGFR status (+++); B – PHB status (from + to +++)



A. № 15641–44(1) × 400.jpg. Status EGFR (+++)

B. № 15641–44(2) × 600.jpg. Status PHB (–/+)

Figure 8. H/IHC No. 15641–44: mature placenta with a positive status of EGFR and PHB,
A –EGFR status (+++); B – PHB status (–/+)

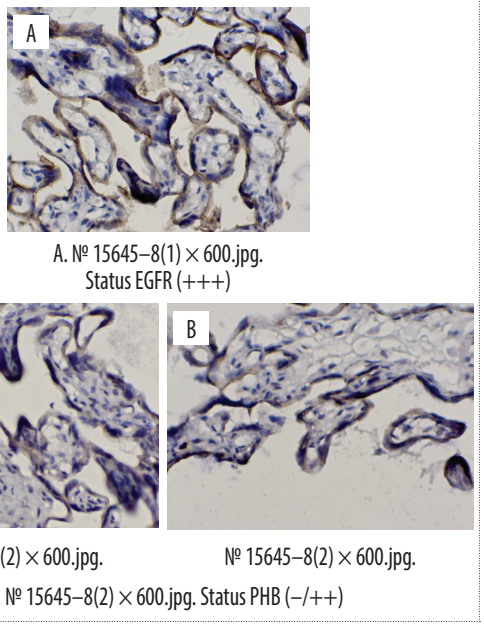


A. № 14009–12(1) × 400.jpg. Status EGFR (+++)

B. № 14009–12(2) × 200.jpg. Status PHB (–)

Figure 9. H/IHC No. 14009–12: pathologically immature placenta, a variant of dissociated chorion maturation, with a positive status of EGFR and a negative status of PHB receptors:
A – EGFR status (+++); B – PHB status (–)

We examined the likelihood of an association between neonatal condition at birth and endothelial dysfunction of marker (EGFR) and mitochondrial marker (PHB) expression in the placenta. It was shown that there is a weak inverse relationship between EGFR expression and Apgar score in the post-COVID



A. № 15645–8(1) × 600.jpg. Status EGFR (+++)

№ 15645–8(2) × 600.jpg.

№ 15645–8(2) × 600.jpg.

B. № 15645–8(2) × 600.jpg. Status PHB (–/++)

Figure 10 H/IHC No. 15645–8. Pathologically immature placenta, a variant of hypervascularized sclerotic villi, with a positive status of EGFR and PHB:
A – EGFR status (+++); B – PHB status (–/++).

group (r(23) = -0.108, p = 0.605985); the relationship is not statistically significant. In the control group, the Pearson correlation coefficient r (19 = 0.5962, p = 0.123993) shows that the relationship between EGF expression and the Apgar score is weak and positive (R^2 = 0.3555).

The relationship between PHB expression and the Apgar score in the post-COVID group is negative, weak, r (24) = -0.0507, R^2 = 0.0026; in the control group between PHB expression and the Apgar scale, the correlation is positive and weak, r (19) = 0.2597, p = 0.777687) (R^2 = 0.0674).

Main points

For the first time the expression of EGF, a protein that stimulates cellular growth and cellular differentiation of the epithelial cover (trophoblast), one of the markers of endothelial dysfunction, was studied in the placenta of women who recovered from COVID-19 during this pregnancy.

For the first time, the expression of PHB a multifunctional pleiotropic protein responsible, including for the stabilization of enzymes, oxidative phosphorylation, differentiation, growth and metabolism of cells – a marker of mitochondrial function, in post-COVID placentas.

Comparative immunophenotyping of "post-COVID" placentas and placentas of healthy women showed that the expression of EGFR in "post-COVID" placentas does not differ from that in healthy women, while the expression of PHB is 6 times higher: it is possible to regard these phenomena as a protective mechanism for the intrauterine fetus. Further research is needed to obtain conclusive data.

DISCUSSION

COVID-19 pandemic and associated complications of pregnancy and childbirth, issues of infection of newborns and direct changes in the placental complex do not lose their relevance. The

placenta is being actively studied as a protective barrier and as a separate provisional organ with its own metabolism, immunological and hormonal characteristics. The development of omics technologies has expanded our knowledge in understanding the pathomechanisms of diseases and is a potential direction in the possibilities of clinical management of the situation [2, 4, 9–11].

The purpose of our research was a comparative study of the histological and immunohistochemical features of "post-COVID" placentas and placentas of apparently healthy women. The task of immunophenotyping was to study the functional features of placentas, namely the expression of multifunctional proteins EGF and PHB, the areas of action of which are cell growth and differentiation, regulation of apoptosis, angiogenesis, mitochondrial respiration, regulation of immunity, etc. [2, 5, 12–15].

Among the characteristics of the examined groups, it is noteworthy that among the participants in the main group there was a higher body mass index compared to the control group ($p = 0.000023$), which is a known risk factor for COVID-19 morbidity in the population. The majority of women fell ill in the 3rd trimester of pregnancy (65.51%), and the dependence of the incidence of COVID-19 infection on gestational age is significant ($F = 148.38358$, $p < 0.00001$), which is consistent with the data of DE Popesku et al. [30]. A likely explanation for this fact is physiological change in the relationship of the chest organs as the gravid uterus enlargement.

Analysis of perinatal outcomes demonstrated a higher incidence of preterm birth and pregnancy loss in the 2nd trimester in women with a COVID history, which is consistent with the data of J. Sisman [9], DA Schwartz et al. [10]. According to them, histopathological examination of placentas showed the presence of focal histiocytic intervillusitis, basal chronic villusitis and other inflammatory changes. It is assumed that the identified inflammation in combination with necrosis of syncytiotrophoblasts in both live-born and stillborn children is a risk factor for preterm birth, transplacental infection of the fetus and perinatal losses [9, 10].

We have found that the clinical assessment of newborns in the post-COVID group is characterized by lower Apgar scale scores, in contrast to the results of Satish Patki. et al., who found no difference in the condition of newborns between children in the compared groups [6]. Thus, out of 55 live-born children from the main group, 28 (50.9%) had a score of 7 points or lower at 1 minute after birth, which was accompanied by a corresponding need for these children to stay in the intensive care unit (10.34%), respiratory support and therapy (5.17%). In the control group at 1 minute, 8 children (20%) received a score of 7 points on the Apgar scale, the remaining 80% were scored at 8–9 points. The results obtained are consistent with the data of SS Foo et al., OM Man et al., who note a high risk of respiratory disorders even in full-term newborns from mothers with COVID-19, and explain this by an imbalance in the cytokine profile pregnant (IFN-λ, IL-1β/IL-18/CASP1, etc.) [7, 8].

Given the conflicting data on the relationship between a COVID history during pregnancy and the Apgar score of newborns, it can be said that, regardless of the condition at birth, these children require long-term clinical monitoring in order to prevent possible risks.

Histopathological characteristics of "post-COVID" placentas, according to our data, showed the presence of tissue hypoxia and chronic placental hypoperfusion. We found in "post-COVID" placentas a higher frequency of MVM in the form of necrotic changes in the trophoblast (internal maternal infarctions – 4.3 times more; the number of syncytial nodules – 5.3 times more) and FVM (chorangiosis and hypovascular chorion – 2.3 times more). Significant difference in the identified patterns is consistent with the data of Popescu D.E. et al. [30], who also found vasculopathy in both the mother (heart attacks – 17% vs 5%) and in the fetus (29%). They also showed the presence of chorioamnionitis in 8.3% of "post- COVID" placentas; we found basal deciduitis (20.69% vs 10%) and lymphoid infiltration of the membranes (17.24%). Intervillous thrombosis (20.69% vs 5%) and increased perivillous fibrin deposition (20.69% vs 12.5%) were found in both groups. Similar results were shown by Popescu D. et al, Levitan D. et al. also reported congestion in the terminal chorionic villi and microchorangiosis in the placentas of women with a history of COVID [3, 30].

It should be noted that one of the most common patterns of "post-COVID" placentas in our study was congestion of the villous vessels (26 samples – 44.82%), intervillous space (18–31.03%), hemorrhage into the basal lamina (11–18, 9%) and fetal membranes (19–32.75%). There are literature data that report the risks of spontaneous hemorrhages in various organs during COVID-19 infection [31].

Hemodynamic disturbances in the feto-placental circulation can apparently be explained as follows. Probably, hypoxia and hypoperfusion of placental tissue caused by COVID-19, together with procoagulant changes in the hemostatic system, are accompanied by necrotic changes in the villous tree with subsequent instability of the vascular wall, which leads to hemorrhages or local congestion without clinical manifestations.

As for the immunophenotyping of "post-COVID" placentas for the expression of EGFR and PHB, we did not find any literature data covering these aspects specifically in pregnant women who have recovered from COVID-19. It is known about the possible role of EGFR in the genesis of endothelial dysfunction in pregnant women with preeclampsia and placental dysfunction [12, 13].

We did not find any differences in the expression of EGF in "post-COVID" placentas and placentas of healthy women ($U_{emp} = 197.5$, $z = 1.18776$, $p = 0.23404$). If we draw parallels between the pathogenetic mechanisms of the development of endothelial dysfunction in pregnant women with preeclampsia and during COVID-19 infection, as well as data that EGFR is not only a binding protein, but is also activated in response to SARS-CoV-2 through mitogen-activated signaling pathway [21], it is possible that sufficient or overexpression of EGFR can be regarded as a protective mechanism that aims to ensure the growth of the placenta and fetus in pregnant women with COVID-19. Our result is consistent with the data of D Escamilla-Illescas et al. [22], who, when studying acute kidney injury in patients with COVID-19, also found overexpression of EGFR, as well as with data from SU Dülger et al. [32], who noted activation of EGFR expression in 78% of patients with varying degrees of pulmonary fibrosis gravity.

This assumption requires further research.

As for the expression of PHB, we found a significant activation of its expression (6 times more than in the control group) in pregnant women with a history of Covid-19 (U_{emp} = 87.5, z = 3.63182, p = 00028). There are isolated literature data indicating an increase in PHB expression in the placentas of women with unexplained recurrent miscarriage [5, 15].

It is known that placental mitochondria are critical for trophoblast function. It is likely that increased expression of PHB in pregnant women with a COVID-19 history can be considered as a protective mechanism aimed at preserving mitochondrial respiration and the metabolic and immunological role of mitochondria [2, 19].

The negative correlation we identified between the Apgar score of newborns and the degree of expression of a marker of endothelial dysfunction (EGFR: r (23) = -0.108, p = 0.605985) and a marker of mitochondrial function (PHB: r (24) = -0.0507) deserves special attention, R^2 = 0.0026) in the group of women with a COVID history. In the placentas of healthy women, PHB expression was determined in most cases "microfocally" – 6 times less. It can probably be assumed that these markers reflect precisely the functional state of the placental complex in pregnant women with a COVID-19 history. There is information in the literature about the mutual necessity of nitric oxide (a unique messenger of intercellular interaction that plays a key role in endothelial dysfunction) and PHB to ensure neuronal resistance to stress associated with hypoxia and hypoglycemia [2, 18]. The authors suggest that this may be one of the mechanisms to explain the neuroprotective function of PHB. We obtained a negative correlation of PHB with the assessment of the "functional" state of newborns at birth, and suggest that an increased level of PHB expression may reflect the risk of impaired adaptive capabilities of children.

Thus, a comparative study of macroscopic, histological features of "post-COVID" and "healthy" placentas and some functional characteristics of placentas using IHC allowed us to draw the following conclusions.

CONCLUSIONS

The rapid spread of COVID-19 and the high mutation ability of the SARS-CoV-2 virus requires careful research to find and understand the role of possible biomarkers in adaptation and changes in the placental complex in pregnant women with a COVID-19 history. This study suggests that SARS-CoV-2 infection during pregnancy is associated with certain changes in placental metabolism and changes in the expression of placental proteins EGFR and PHB may be involved in the pathogenetic mechanisms of the development of placental dysfunction. The limited sample size requires additional research, but nevertheless, the results of our study offer new biomarkers in assessing the functional characteristics of the placenta in pregnant women with COVID-19 infection.

Strength & limitation

For the first time, immunophenotyping was performed to study the functional characteristics of "post-COVID" placentas, namely the expression of EGFR and PHB, which suggested that COVID-19 infection does not affect cell proliferation and differentiation, angiogenesis in the placenta, but is characterized by hypersecretion of a marker of placental function mitochondria, which may be evidence of hypoxia/ischemia of the placenta.

The likelihood of a relationship between the condition of newborns at birth and the expression of a marker of angiogenesis and endothelial dysfunction (EGF) and a mitochondrial marker (PHB) in the placenta was studied and their correlation with Apgar scores was found.

Weaknesses of the study include the limited sample size and the possible lack of placental testing for SARS-CoV-2, which could provide additional information about the interdependence of the results: only mothers were tested.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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IMMUNOHISTOCHEMICAL ASSESSMENT OF EPIDERMAL GROWTH FACTOR RECEPTOR AND PROHIBITIN EXPRESSION IN "POST-COVID" PLACENTAS: RESULTS OF A COMPARATIVE CROSS-SECTIONAL STUDY

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Background. COVID-19 pandemic is accompanied by a considerable number of morbidity cases among pregnant women. Certain knowledge has been accumulated about the histopathological features of the placenta during SARS-CoV-2 infection. Specific proteomic studies of the function of the placenta are insufficient.

Objective of the study: to study the perinatal outcomes of pregnancy and histopathological features of the placenta and the expression of epidermal growth factor receptors (EFGR) and prohibitin (PHB) in the placenta in pregnant women with COVID-19 infection in comparison with data in a group of healthy pregnant women without a COVID-19 history.

Materials and methods. 58 pregnant women with COVID-19 infection during pregnancy and 40 healthy pregnant women were examined at the base of Maternity Hospital No. 2 of the Odessa City Council. A histological and immunohistochemical study of placentas was carried out for the expression of EFGR and PHB In addition to a general clinical examination.

Results. A higher frequency of premature births (15.51% vs 5%) and cesarean sections (34.4% vs 12.5%) in the "post-COVID" group was revealed. Most women fell ill in the third trimester of pregnancy (65.51%). A significant difference was found in Apgar scores in the groups (6.48 ± 2.39 vs 8.05 ± 0.54 points), in the weight of newborns (3067.93 ± 620.21 g vs 3617.25 ± 354.58 g). In the placentas of the "post-COVID" group, signs of mother's (53.45% vs 12.5%) and fetus' vascular malperfusion (32.7% vs 15%) were detected with greater frequency; as well as hemodynamic disturbances (53.45% vs 15%). Analysis of EFGR expression in the groups showed no differences (2.96 ± 0.2 vs 2.75 ± 0.44) in contrast to PHB (1.52 ± 1.12 vs 0.25 ± 0.5), which was characterized by overexpression in the women with COVID-19.

Conclusions. SARS-CoV-2 infection during pregnancy is associated with certain changes in placental metabolism, and changes in the expression of placental proteins EGFR and PHB may be involved in the pathogenetic mechanisms of the placental dysfunction development. The limited sample size requires additional research.

Keywords: pregnancy, COVID-19, immunohistochemical study of the placenta, epidermal growth factor, prohibitin.

ІМУНОГІСТОХІМІЧНА ОЦІНКА ЕКСПРЕСІЇ РЕЦЕПТОРА ЕПІДЕРМАЛЬНОГО ЧИННИКА РОСТУ ТА ПРОГІБІТИНУ В «ПОСТКОВІДНИХ» ПЛАЦЕНТАХ: РЕЗУЛЬТАТИ ПОРІВНЯЛЬНОГО ПОПЕРЕЧНОГО ДОСЛІДЖЕННЯ

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Обґрунтування. Пандемія COVID-19 пов'язана з чималою кількістю випадків захворюваності серед вагітних. На сьогодні накопичено певні знання щодо гістопатологічних особливостей плаценти за інфекції SARS-CoV-2. Специфічних досліджень щодо функціональних властивостей плаценти протеомного спрямування наразі проведено недостатньо.

Мета дослідження: вивчити перинатальні наслідки вагітності, гістопатологічні особливості плаценти та експресію рецепторів епідермального чинника росту (EFGR) і прогібітину (PHB) у плаценті вагітних, інфікованих COVID-19, порівняно зі здоровими вагітними без ковідної інфекції в анамнезі.

Матеріали та методи. На базі КНП «Пологовий будинок №2» Одеської міської ради обстежено 58 вагітних з інфекцією COVID-19 та 40 здорових вагітних. Окрім загальноклінічного обстеження проведені гістологічне та імуногістологічне дослідження плацент на предмет експресії EFGR та PHB.

Результати. Виявлено більшу частоту передчасних пологів (15,51 проти 5%) та кесаревих розтинів (34,4 проти 12,5%) у «постковідній» групі порівняно зі здоровими вагітними. Більшість жінок захворіли у III триместрі вагітності (65,51%). У вагітних із ковідною інфекцією та без виявлено вірогідну різницю за показниками шкали Апгар (6,48 ± 2,39 проти 8,05 ± 0,54 бала) та у вазі новонароджених (3067,93 ± 620,21 проти 3617,25 ± 354,58 г). У плацентах «постковідної» групи з більшою частотою виявлялися ознаки судинної мальперфузії матері (53,45 проти 12,5%) та плода (32,7 проти 15%); порушення гемодинаміки (53,45 проти 15%). Аналіз експресії EFGR у групах не показав відмінностей (2,96 ± 0,2 та 2,75 ± 0,44) на відміну від PHB (1,52 ± 1,12 та 0,25 ± 0,5), який характеризувався гіперекспресією в групі вагітних, хворих на COVID-19.

Висновки. SARS-CoV-2 інфекція під час вагітності асоціюється з певними змінами у метаболізмі плаценти, а зміна експресії плацентарних білків EGFR та PHB може бути залучена до патогенетичних механізмів розвитку плацентарної дисфункції. Обмежений розмір вибірки потребує додаткових досліджень.

Ключові слова: вагітність, COVID-19, імуногістохімічне дослідження плаценти, епідермальний фактор росту, прогібітин.