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COMPARATIVE ANALYSIS OF HISTOPATHOLOGICAL FEATURES OF “POST-COVID” PLACENTAS AND PLACENTAS OF HEALTHY WOMEN WITH PHYSIOLOGICAL COURSE OF PREGNANCY

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Summary. Manasova G. S., Stasy Ya. A., Sitnikova V. A. **COMPARATIVE ANALYSIS OF THE HISTOPATHOLOGICAL FEATURES OF “POST-COVID” PLACENTAS AND PLACENTAS OF HEALTHY WOMEN WITH A PHYSIOLOGICAL COURSE OF PREGNANCY.** – *The Odessa National Medical University; e-mail: gulsymmanasova@gmail.com.* The impact of COVID-19 on the course of pregnancy and perinatal outcomes continues to be actively studied, and one of the directions is the study of the morphology of the placental complex. We studied the histopathological features of “post-Covid” placentas (n = 58) in comparison with the placentas of healthy women (n = 40), taking into account the recommendations of the Amsterdam Placental Workshop Group. A clinical examination of women was carried out on the basis of the “Maternity Hospital No. 2” (Odessa), and a pathomorphological examination was carried out at the Odessa Regional Pathological Bureau. In “post-Covid” placentas, signs of maternal vascular malperfusion (OR = 21.722, 95%CI 7.409 63.684, P <.05) and “silent” hemodynamic disorders in both the maternal and fetal sections were significantly more often detected (OR = 6.506, 95% CI 2.370 17.858, P<.05). Signs of chronic inflammatory pathology were also revealed (lymphoid infiltration of the fetal membranes - F = 0.5807, OR = 1.458, 95%CI 0.458 81.777, P <.05). The identified features of “post-Covid” placentas are not specific: general possible hypoxia and tissue hypoperfusion under the conditions of a systemic inflammatory process in the mother, can affect the morpho-functional state of the placenta. Further research is required to understand how these placental features may influence perinatal pregnancy outcomes and long-term outcomes in children.

Key words: COVID-19, placenta’s histopathological feature, physiological course of pregnancy.

Реферат. Манасова Г. С., Стасій Я. А., Ситнікова В. А.. **ПОРІВНЯЛЬНИЙ АНАЛІЗ ГІСТОПАТОЛОГІЧНИХ ОСОБЛИВОСТЕЙ «ПОСТКОВІДНИХ» ПЛАЦЕНТ ТА ПЛАЦЕНТ ЗДОРОВИХ ЖІНОК З ФІЗІОЛОГІЧНИМ ПЕРЕБІГОМ ВАГІТНОСТІ.** – Одеський національний медичний університет. Вплив COVID-19 на перебіг вагітності та перинатальні результати продовжує активно вивчатися, одним із напрямків є дослідження морфології плацентарного комплексу. Ми вивчали гістопатологічні особливості «постковідних» плацент (n = 58) у порівнянні з плацентами здорових жінок (n = 40), враховуючи рекомендації Amsterdam Placental Workshop Group. Диспансерне обстеження жінок проводилось на базі «Пологового будинку № 2» (м. Одеса), а патоморфологічне

обстеження – в Одеському обласному патологоанатомічному бюро. У «постковідних» плацентах достовірно частіше виявлялися ознаки мальперфузії судин матері (OR = 21,722, 95% CI 7,409 63,684, P <.05) і «тихих» гемодинамічних розладів як у материнській, так і в плодовій частинах (OR = 6,506, 95% ДІ 2,370 17,858, P<0,05). Виявлено також ознаки хронічної запальної патології (лімфоїдна інфільтрація плодових оболонок - F = 0,5807, OR = 1,458, 95% ДІ 0,458 81,777, P <.05). Виявлені ознаки «постковідних» плацент неспецифічні: загальна можлива гіпоксія та гіпоперфузія тканин за умов системного запального процесу у матері можуть впливати на модрофункціональний стан плаценти. Потрібні подальші дослідження, щоб зрозуміти, як ці особливості плаценти можуть впливати на перинатальні результати вагітності та віддалені результати у дітей.

Ключові слова: COVID-19, патогістологічні особливості плаценти, фізіологічний перебіг вагітності.

Introduction

Acute respiratory coronavirus infection COVID-19, despite certain advances in treatment and prevention, continues to spread and is accompanied by a wide range of clinical manifestations. Epidemiological and genetic changes of the SARS-CoV-2 coronavirus from the moment of aggravation to the present have generally led to milder symptoms of acute respiratory viral infection (ARVI), which, however, can be accompanied by a severe course with multiple organ failure and death [1].

The influence of SARS-CoV-2, an associated coronavirus infection, on the course of pregnancy and the condition of the intrauterine fetus and newborn remains the subject of debate, although the dominant opinion is that COVID-19 is more severe in pregnant women compared to non-pregnant ones, in particular, we are talking about a higher incidence of preeclampsia, premature birth, and stillbirth. These patients are more likely to require intensive care (IC) compared to non – infected women [2, 3, 4].

During physiological pregnancy, the placental barrier strictly regulates the exchange of endogenous and exogenous materials between mother and fetus, including protecting the fetus from mother's infections and diseases [5].

The main structural element and regulator of the formed placenta functions is the syncytiotrophoblast lining the villi. It is the syncytiotrophoblast and the endothelium of the fetal capillaries, separated by a thin interstitium, constitute a multilayer membrane that provides the barrier function of the placenta. This specialized barrier not only separates the intervillous space of the mother and the fetal circulation, but is also responsible for the selectivity and regulation of the rate of transplacental transport. It also plays a key role in autophagy and the prevention of the movement of pathogens from the maternal circulation to the fetal circulation, including in the resistance of the placental-fetal unit to viral infections. Aberrant changes in its structure and function lead to vascular and metabolic disorders in the maternal (maternal vascular malperfusion - MVM) and/or fetal (fetal vascular malperfusion - FVM) parts with subsequent pregnancy complications [6, 7].

Studies of “post-Covid” placentas have shown the presence of certain nonspecific inflammatory, thrombotic and vascular changes, which are also found in the case of other pathologies [8]. This suggests that SARS-CoV-2 is an associated acute respiratory viral infection (SARS-CoV -2 – associated ARVI) not only causes certain changes in the placenta, but can also lead to unfavorable perinatal outcomes and long-term multisystem defects in children exposed to intrauterine influence of coronavirus infection.

Morphological changes in “Covid” placentas can be characterized by both maternal and fetal vascular malperfusion [9].

Currently, knowledge about “post- Covid” placentas with a description of the histomorphological features of this provisional organ during SARS-CoV-2 continues to be accumulated. Studying the course of the disease itself and structural and functional changes in the placenta, as well as the impact that these changes on the course and outcome of pregnancy, continues to remain a high priority. These studies and the knowledge gained are of decisive medical and social importance for pregnant women and their children, not only at the end of

pregnancy, but also in the long term [10].

The purpose: to perform a comparative research of the morphohistological features of the placentas of women who had COVID-19 during pregnancy (“post-Covid” placentas) and the placentas of **conditionally** healthy women.

Materials and methods. During a cross-sectional descriptive cohort study, the placentas of 58 women who had COVID-19 coronavirus infection during pregnancy were studied (main group); The control group included 40 conditionally healthy women with a physiological pregnancy.

The study was conducted in accordance with the standards of good clinical practice (approved by the Bioethics Commission of the Odessa National Medical University) and the requirements of the Declaration of Helsinki.

All patients signed informed consent to participate in the study. The work is 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 No 0122 U201370.

Clinical observation and examination of the women was carried out from 01.11.2021 until 12.31.2022 on the basis of the “Maternity Hospital No. 2” of the Odessa City Council. The latter is a 2nd level institution for the provision of obstetric and gynecological care, one of its units a hospital base for providing medical care to pregnant women diagnosed with COVID-19, residents of Odessa city and the Odessa region.

The main group included pregnant women hospitalized for delivery with a diagnosis of COVID-19 at the time of admission or undergoing hospital treatment due to **SARS-CoV-2-ac. ARVI** in the first or second trimester of pregnancy, i.e. those who had a confirmed “Covid” history. Patients were excluded from the control group if they had extragenital pathology (preeclampsia, fetal growth restriction, chronic arterial hypertension, diabetes, coagulopathy or thrombophilia), which could affect the anatomical and functional features of the placenta.

To verify COVID-19, at the first stage, a rapid test for coronavirus was performed in the emergency department of the maternity hospital, based on the detection of the SARS-CoV-2 nucleocapsid protein (antigen) in a smear-scraping from the back wall of the pharynx and nose using the ICA method (immunochromatographic analysis). The final diagnosis of COVID-19 was based on detection of SARS-CoV-2 virus RNA using real-time polymerase chain reaction (PCR). Selection of samples (swabs and scrapings from the back wall of the pharynx and nose) for testing using the PCR method and transportation to a certified laboratory was carried out in accordance with the requirements of regulatory documents of the Ministry of Health of Ukraine.

The severity of the disease was classified based on the order of the Ministry of Health of Ukraine dated March 28, 2020 No 722 “Organization of medical care for patients with coronavirus disease (COVID-19)” with amendments dated January 7, 2021 No. 10 “On approval of Amendments to the Standards of Medical Care “Coronavirus Disease (COVID-19).” Before hospitalization in the maternity hospital, pregnant women, according to the patient route developed by the Department of Health of the Odessa City Council, underwent an X-ray or CT examination of the chest organs in a multidisciplinary hospital.

The study analyzed data on clinical manifestations, maternal and perinatal outcomes. All patients underwent a standard general clinical examination (general blood and urine tests, etc.), as well as the level of D-dimers, C-reactive protein in the blood (quantitative method), biochemical blood test (bilirubin and its fractions, protein, creatinine, urea, etc.).

The placentas of both groups patients after childbirth were sent for macroscopic and microscopic histopathological examination to the Odessa Regional Pathanatomical Bureau (in accordance with an agreement with this enterprise) after preliminary fixation in a 10% formalin solution. Mophrological examination of placentas was carried out taking into account the requirements of regulatory documents of the Ministry of Health of Ukraine. To describe histopathological changes, the recommendations of the Amsterdam consensus statement of the International Federation for the Study of the Placenta were used [11].

After macroscopic assessment and morphometry, pieces of placental tissue were taken for microscopic examination - 8 points from each placenta (areas measuring 1*1 cm; 2 sites from the central, paracentral and marginal parts of the placenta, 1 strip of fetal membranes 8 cm long, 1

piece of umbilical cord. The material was fixed in a 10% formalin solution, dehydrated in 4 solutions of alcohols of various strengths, in 2 solutions of chloroform of various concentrations, then in 2 containers of paraffin with base wax. Sections were prepared on a sled microtome, stained with hematoxylin-eosin, covered with polystyrene and examined at magnifications 10x10, 10x20 and 10x40; LEICA DMIS microscope was used.

Statistical assessment of the research results, including descriptive statistics, calculation of the relative extensive percentage indicator, was carried out using the licensed programs “Microsoft Exell” and “Social Science Statistics” (<https://www.socscistatistics.com/tests/>); Fisher's exact test, chi-square test (χ^2), odds ratio, calculation of 95% confidence interval and relative risk were also calculated.

Results. According to demographic and anthropometric indicators, the groups were homogeneous in terms of basic indicators. All women in both groups were of Slavic ethnicity; According to professional affiliation (mental labor, physical labor, housewives: $\chi^2 = 1.3676$, $p = 504703$, $p > .05$), no significant differences were found between pregnant women in the surveyed groups.

The average age of women was 29.21 ± 4.3 vs 30.35 ± 3.12 years in the main and control groups ($t = 0.21$, $p = 0.830553$). Rural women in the main group accounted for 34.45% ($n = 20$), and the urban ones – 65.51% ($n = 38$) versus 20% ($n = 8$) and 80% ($n = 32$ – in the control group ($F = 0.17198$, $RR = 0.82$, $OR = 0.475$, 95% CI 0.185 1.222, $p > .05$).

The average BMI in the main group was greater than in the control group (27.32 ± 4.48 vs 22.8 ± 2.30 kg/m^2 ; $p = .000023$, $p < 0.05$)

Most of the women from the main group fell ill with COVID-19 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). The average gestational age is 29.6 ± 9.1 weeks. The difference in the incidence rate depending on the stage of pregnancy was significant for each trimester ($f = 148.38358$, $p < .00001$).

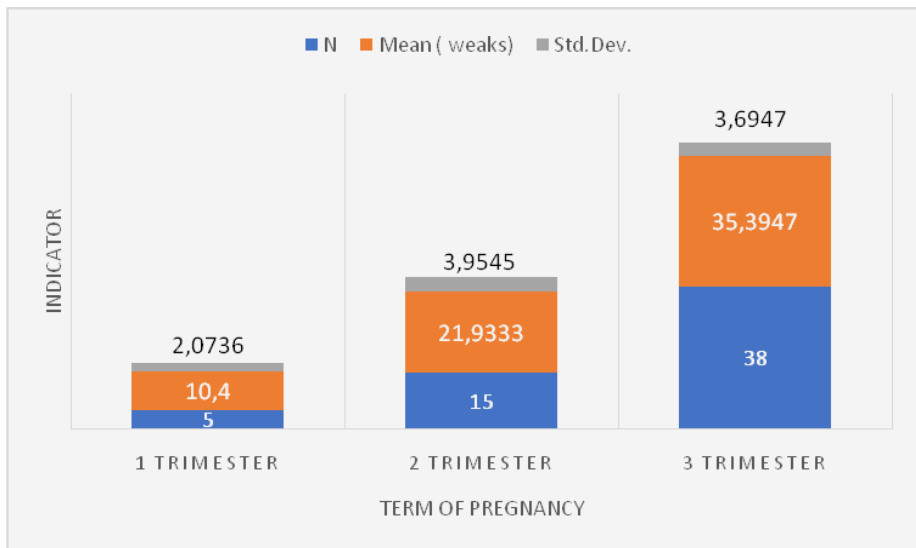


Fig.1. Incidence of COVID-19 in pregnant women by trimester of pregnancy

When analyzing the timing of pregnancy completion in groups, attention is drawn to the high frequency of both premature births (main group: 9 (15.51%) vs control group: 2 (5%) and cases of termination of pregnancy in the 2nd trimester (main group: 3 (5.17%) in women with “Covid” history ($RR = 4.14$, $OR = 4.957$, 95%CI 1.044 25.526), as well as a higher frequency of abdominal delivery ($OR = 1.638$, 95% CI 0.522 5.144).

Macroscopic characteristics of the placentas in the groups did not show significant differences between the groups (Table 1).

Table 1

Morphometric and macroscopic features of post-covid placentas and placentas of healthy pregnant women

Variable	Main group, n=58	Control group, n = 40	P value
Placental weight (g), (M ±σ)	433.79 ± 106.12	493.32 ± 74.07	t=0.46, p=0.646568
Cordinsertion			
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
Structural features of the umbilical cord			
Hypercoil, (n, %)	8 (13.79)	6 (15)	F = 1, p >0.05
Lack of Wharton' jelly, (n, %)	10 (17.24)	3 (7.5)	F = 0.22901

The differences between the groups in the degree of placenta maturity were significantly significant: X2 test (1, N = 98) = 32.99, p = 0.00001 (Table 2).

Table 2

Characteristics of placentas according to the degree of maturity in pregnant women with a "Covid" history and in apparently healthy pregnant women

	Morphologically mature placenta	Morphologically immature placenta	Dissociated maturation of the chorion	Pathological immaturity of the placenta	Row Totals
Pregnant women with "COVID" anamnesis	9 (21.31) [7.11]	3 (4.14) [0.32]	32 (21.31) [5.37]	14 (11.24) [0.68]	N = 58
Healthy pregnant women	27 (14.69)[10.31]	4 (2.86) [0.46]	4 (14.69) [7.78]	5 (7.76) [0.98]	N = 40
Column Totals	36	7	36	19	98 (Grand Total)

Histological characteristics of the placentas indicated the presence of certain statistically significant distinctive features in the placentas of women with a "Covid" history; where the main changes concerned the maternal part of the uteroplacental system (Table 3). In "post-Covid" placentas, pseudoinfarctions, "white" placental infarctions were detected with a significantly higher frequency (OR = 8.037, 95% CI 2.75823.423, p<.05), as well as agglutination of the villous chorion with an increase in the number of syncytial nodules (OR = 21.722, 95 % CI 7.40963.684, p<.05). Fetal vascular malperfusion was evidenced by the presence of crowded avascular or hypovascular villi in the placentas of women in the main group (F = 0.0097, p<.05); this pattern was not found in the control group. Among other pathological patterns, the most significant are hemodynamic disorders in the maternal and fetal sections (OR = 6.50695% CI 2.370 17.858, p <.05.) in the form of congestion of the villous vessels, hemorrhages in the intervillous space, in the decidua plate, in the fetal membranes and in Wharton's jelly umbilical cord (OR = 10.174, 95% CI 1.266 4.645, P>.05).

Table 3

Pathological patterns of the placenta in pregnant women with a “covid” history and in relatively healthy women with a physiological course of pregnancy

Indicator	Main group, n= 58		Control group, n = 40		P value
	абс. ч.	%	абс. ч.	%	
Maternal Vascular Malperfusion - MVM					
Villous infarction (pseudo-infarction, white infarction)	31	53.45	5	12.5	F=0, p<.05, OR = 8.037 95% CI 2.75823.423
Agglutination of villi with a large number of costistincytial cells	46	79.31	6	15	F < 0.00001, p<.05 OR=21.722 95%CI 7.40963.684
Decidual arteriopathy	4	6.90	3	7.5	X ² (1, N = 98) = 0.013, p =.909233. F=1, p >.05
Fetal Vascular Malperfusion – FVM					
Accumulated vascular/hypovascular villi	5	8.62	0	0	F = 0.0097, p<.05
Hyperspiral umbilical cord	4	6.90	0	0	F=0.1428, p>.05.
Chorangiosis (compensatory villous angiomas)	14	24.14	6	15	X ² (1, N = 98) = 1,217; p = .269953, F=0.3164, p >.05, OR =1.803 95% CI 0.627 5.183
Acute inflammatory pathology (AIP), including maternal or fetal inflammatory reaction					
Serous basal deciduitis, Parietal amnionitis	12	20.69	4	10	F= 0.1789, p>.05 RR = 2.07, OR = 2.348 95% CI 0.698 7.895
Unevenly expressed polymorphoclitin infiltration of fetal membranes	5	8.62	3	7.5	F=1, P >.05
Chronic inflammation pathology (CIP), including chronic inflammation or low-grade chronic deciduitis with plasmatic cells					
Lymphoid infiltration of fetal membranes	10	17.24	5	12.5	F=0.5807, P <.05 RR = 1.35, OR =1.458 95%CI 0.458 81.777
Other pathological patterns of placenta					
Deposition of calcium salts in villi	18	31.03	10	25	F=0.65, RR=1.24, OR = 1.35, 95%CI 0.545 3.342
Bleeding in Wharton’s jelly	12	20.69	1	2.5	F=0.0129, P >.05 OR =10.174 95%CI 1.266 4.645
Hemodynamic impairment	31	53.45	6	15	F=0.0001, p < .05. OR =6.506 95%CI 2.370 17.858
Intervillous thrombosis	12	20.69	10	25	F=0.6307, p >.05.
Increase in perivillous fibrin	12	20.69	5	12.5	F=.08184, p>.05
Swelling of Wharton’s jelly	17	29.31	10	25	F=.08184. p > .05.

Note. Hemodynamic disturbances: congestion of villous vessels (26 – main group), presence of blood in the intervillous space (18 – main group), hemorrhage in the basal lamina (11 – main group, 1 – control group), hemorrhage in the fetal membranes (19 – main group, 4 – control group). Reven significance <0.05.

High Lights

The structural features of “post-Covid” placentas are characterized by the presence of histological changes compared to the placentas of relatively healthy women with a physiological pregnancy.

The most significant histological patterns include maternal vascular malperfusion and hemodynamic disturbances in the maternal and fetal placentas, but they are not specific.

Discussion

The risks of multiple organ pathological changes development, typical for COVID-19 during pregnancy can be critically high due to disruption of the barrier function of the placenta involved in the systemic inflammatory process [1, 4, 7].

Most viral infections are characterized by the ability of the virus to overcome the placental barrier and infect the intrauterine fetus, often with the development of a generalized inflammatory process and pronounced clinical and morphological manifestations up to its intrauterine death [12, 13]. As for coronavirus infection, the question of violation of the placental barrier and damage to the placenta remains debatable [8, 14, 15], which became the rationale for our study. During the work, the pathohistological patterns of “post-Covid” placentas were studied in comparison with those in the placentas of apparently healthy women with a physiological course of pregnancy.

According to the results of the study, the general morphometric and macroscopic characteristics of the placentas in the groups did not have significant differences in placental mass, location or structure of the umbilical cord, which is consistent with the data of Corbetta-Rastelli CM et al. (2023) and contradicts the study of Radan A Petal (2022), who identified a lower weight of “post-Covid” placentas and believe that the risk of low placental weight does not depend on the stage of pregnancy with infection occurred [16]. It is known that there is a positive correlation between the weight of the placenta and the weight of newborns, which, as the gestation period increases, changes towards a decrease in the placental-fetal ratio [17]. It is likely that the impact of coronavirus infection is not always accompanied by a decrease in placenta’s weight and violation of its functional properties, which can be explained by the peculiarities of its hormonal and biochemical function [18].

When analyzing the degree of placenta’s maturity, we revealed the presence of significant differences in the groups. In healthy women, a morphologically mature placenta was determined 4.35 times more often than in the “Covid” group (67.5% vs 15.51%); whereas dissociated chorion maturation (DCM) was observed 5.6 times more in women of the main group (55.17% vs 10%), and pathological immaturity of the placenta was 1.93 times more often (24.14% vs 12.5%).

According to some data, DCM and pathological immaturity of the villi may be associated with the risk of intrauterine growth retardation and fetal death, with metabolic disorders in the mother, obesity and other pathological conditions [19, 20]. In general, most researchers note that the interpretation of the morphology of villous maturation, therefore, chorion is quite subjective.

In our study, with a variant of DCM, pathologist had described that along with normal terminal villi, there are areas of embryonic villi and small fibrin thrombi in the placentas intervillous space. Moderate villous angiomatosis, numerous syncytial nodules, as well as hemodynamic disturbances in the form of congestion of villous vessels, focal hemorrhages in the chorionic plate, in the fetal membranes and Wharton's jelly of the umbilical cord were also revealed.

The described changes are not specific and it can probably be assumed that SaRS-Cov-2 associated **viremia** may act as a possible trigger for increased cytokine production with the development of generalized endotheliopathy, which can occur directly in the placenta or be caused by hypoxemia in the mother [9]. The likelihood of the intrauterine fetus damage most likely depends on the severity of the disease and the development of multiple organ failure syndrome, which also involves the placenta.

We also found that the longer the pregnancy, the greater is the likelihood of COVID-19 morbidity. In the 3rd trimester, the incidence is 3 times higher than in the 1st trimester, and 2 times higher compared to the 2nd trimester, which is consistent with the findings of Corbetta-Rastelli CM et al., (2023) [8]. This fact can be explained by physiological changes in the ratio of the chest and abdominal organs as pregnancy progresses and the growth of the uterus with corresponding changes in the respiratory volume of the lungs.

According to our results, the most common histological pattern of “post-Covid” placentas is MVM (pseudoinfarctions, villous agglutination, increased number of syncytial nodules). In this group it was detected 4.3 times more often than in the control group. Lin R. et al. (2023) noted the presence of MVM in 27.1% of studies and did not find a relationship between the gestational age of infection and changes in the placenta, and Corbetta-Rastelli CM et al. (2023) concluded that the most severe malperfusion of the maternal part of the placental circulation is observed with infection in the second and third trimesters of pregnancy (69% of 131 patients) [8]. According to Garg R. et al. (2023), signs of MVM in the form of an increase in the number of syncytial nodes and fibrinoid necrosis were observed in 100% of “covid” placentas [21]. It can probably be assumed that MVM reflects a maternal systemic inflammatory process, which may be limited by the placental barrier, since the frequency of fetal vascular malperfusion, according to our data, is detected less frequently.

Thus, FVM in the form of clusters of avascular villi was detected in 8.62% of placentas in women from the “Covid” group; they also had compensatory villous angiomatosis or chorangioma 1.6 times more often than in the control group. Literature data suggests a higher incidence of vascular damage to the fetal part of the placenta under conditions of severe COVID-19. Lin R. et al. (2023) reported 15.1%, Patberg ET et al. (2020) reported about 32.5%, Glynn SM et al., (2022) – about 53.8% cases of FVM detection [14, 22, 23]. We assume that it is precisely with the severity of the main disease such a high frequency of damage to the fetal part of the placenta is associated, when we can already talk about damage to the placental barrier.

As for inflammatory reactions in the placentas of women with a “Covid” history, we did not find a significant difference in the frequency of “expected” acute or chronic inflammation, although the probability of inflammation is 2.3 times higher compared to the control group (OR = 2.348. 95% CI 0.698 7.895). According to the literature, signs of inflammation in the form of villitis or eosinophilic T-cell vasculitis or lymphoid infiltration or villitis, rich in plasma cells, etc., in “Covid” placentas are detected in 54.8%–5.2% of the studied placentas [14, 15]. So, the information is quite different, which indicates insufficient knowledge of the problem, including from the point of view of defining the histological picture.

Analysis of other pathological patterns of placentas showed a high probability of metabolic disorders in “Covid” placentas in the form of villous calcification, but this was not a significant pattern, which is consistent with literature data [21, 24]. Placental calcification can be the result of both exposure to infection and hypoxia or systemic stress, the combination of which are inherent in the covid history of the women examined.

The most common pathohistological patterns in the studied “post-Covid” placentas, according to the results of our study, were hemodynamic disorders (hemorrhages), the probability of which was 6.5 times greater compared to healthy pregnant women. These were patterns in the form of congestion of the villous vessels, hemorrhages in the intervillous space, in the basal lamina, in the fetal membranes, as well as in the Wharton’s jelly of the umbilical cord, i.e. we are talking about the involvement of both maternal and fetal structures. Joshi B et al. (2022) in their study (179 participants) also found an increased incidence of retroplacental clots/hemorrhages and attributed this phenomenon to “silent” antepartum hemorrhages caused by COVID-19 [25].

Other authors have also reported a high risk of antenatal (silent) and postnatal bleeding in pregnant women with a history of Covid [26, 27]. This information rather aggravates the problem of treating pregnant women with COVID-19, as it raises doubts about the use of anticoagulants in complex therapy [28]. The detected “silent” antenatal hemorrhages, on the one part, did not seem to lead to the expected negative consequences (placental abruption, intrauterine bleeding) and can be attributed specifically to “findings”; on the other part, generally accepted thromboprophylaxis for COVID-19 can be considered with fear of increasing or provoking massive bleeding during pregnancy or after childbirth.

Conclusions. Thus, a comparative morphohistological study of “post-Covid” placentas and placentas of conditionally healthy women with a physiological course of pregnancy allowed us to draw some conclusions.

Histological patterns in “post-Covid” placentas demonstrate a higher prevalence of maternal vascular malperfusion compared to fetal vascular malperfusion, however, these changes are not specific and may not be directly related to COVID-19 infection. No “post-Covid” placentas

were identified “expected” frequency of acute or chronic inflammatory changes.

The systemic inflammatory process and direct maternal hypoxia in the context of COVID-19 may likely contribute to the vulnerability of the placental barrier to both the virus itself and bacterial infection. Hypoperfusion/ischemia/hemorrhage, nonspecific inflammatory changes in the placental complex under these conditions may indicate activation of the nonspecific humoral immune system and affect the morpho-functional state of the placenta. Further research is required, including the study the hemodynamic and metabolic characteristics of the utero-placental-fetal system to obtain an evidence base and optimize the management of pregnant women with a “Covid” history.

Authors Contributions

Authors declare about equal contribution.

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Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board (or Ethics Committee) of the Odessa National medical University (7/119/2018, 27 December 2018).

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Data Availability Statement

The data presented in this study are available on request from the corresponding author.

Conflicts of Interest

The authors declare no conflict of interest.

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ОСОБЛИВОСТІ СЕСТРИНСЬКОГО АМБУЛАТОРНОГО СПОСТЕРЕЖЕННЯ ЗА ХВОРИМИ НА ХРОНІЧНУ СЕРЦЕВО-СУДИННУ ПАТОЛОГІЮ З УРАХУВАННЯМ НАСЛІДКІВ ПАНДЕМІЇ КОВІД-19 ТА СТАНУ ХРОНІЧНОГО СТРЕСУ В УМОВАХ ВІЙНИ

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Summary. Abdullaeva I. V., Valetskyi Yu. M., Kalinchuk S. V. **FEATURES OF NURSING OUTPATIENT OBSERVATION OF PATIENTS WITH CHRONIC CARDIOVASCULAR PATHOLOGY TAKING INTO ACCOUNT THE CONSEQUENCES OF THE PANDEMIC COVID-19 AND THE STATE OF CHRONIC STRESS IN THE CONDITIONS OF WAR.** - *Communal institution of higher education "Volyn Medical Institute", Lutsk; e-mail: waletski@gmail.com.* The issue of developing an effective model of dispensation and outpatient support for patients with cardiovascular pathology is urgent. An analysis of the occurrence of cardiovascular complications in patients who have experienced severe or moderate forms of COVID-19 and post-covid syndrome, who are in a state of chronic stress, shows that the frequency of these complications depends directly on the quality of the patient's implementation of the cardiologist's recommendations at the outpatient stage of treatment and observation.

ЗМІСТ	CONTENT
НОВИНИ МІЖНАРОДНОЇ АСОЦІАЦІЇ МОРСЬКОЇ МЕДИЦИНИ (ІМНА)	IMHA's NEWS
ПРО ПІДСУМКИ РОБОТИ XVI МІЖНАРОДНОГО СИМПОЗИУМУ З МОРСЬКОЇ МЕДИЦИНИ3	16 INTERNATIONAL SYMPOSIUM ON MARITIME HEALTH- A MARITIME HEALTH ODYSSEY IN ATHENS3
МЕДИЦИНА НЕВІДКЛАДНИХ СТАНІВ	EMERGENCY MEDICINE
<p>Майданюк В. П., Тодуров І. М. Печиборщ В. П., Якимець В. М. Волянський П. Б., Вороненко В. В. Власенко О. М., Якимець В. В. Печиборщ О. В., Бабій В. П. Поспелов О. М. НАСЛІДКИ ТЕРОРУ В УКРАЇНІ ТА МЕДИЧНИЙ ЗАХИСТ7</p>	<p>Maydanyuk V. P., Todurov I. M. Pechiborshch V. P., Yakymets V. M. Volyanskyi P. B., Voronenko V. V. Vlasenko O. M., Yakymets V. V. Pechiborshch O. V., Babiy V. P. Pospelov O. M. CONSEQUENCES OF TERROR IN UKRAINE AND MEDICAL PROTECTION.....7</p>
<p>Савицький І. В., Гавриченко Д. Г. Гончарова Л. В., Дімова А. А. Комлевой О. М., Федоренко Т. В. ПАТОГЕНЕТИЧНА РОЛЬ ПЕРОКСИДНИХ МЕХАНІЗМІВ ПРИ ХРОНІЧНОМУ СТРЕСІ ЗА УМОВ ГІПОФУНКЦІЇ ЩИТОПОДІБНОЇ ЗАЛОЗИ19</p>	<p>Savytskyi I. V., Gavrichenko D. G. Goncharova L. V., Dimova A. A. Komlevoi O. M., Fedorenko T. V. PEROXIDE MECHANISMS PATHOGENETIC ROLE IN CHRONIC STRESS IN CONDITIONS OF THYROID GLAND HYPOFUNCTION 19</p>
COVID-19	COVID-19
<p>Манасова Г. С., Стасій Я. А. Ситнікова В. А.. ПОРІВНЯЛЬНИЙ АНАЛІЗ ГІСТОПАТОЛОГІЧНИХ ОСОБЛИВОСТЕЙ «ПОСТКОВІДНИХ» ПЛАЦЕНТ ТА ПЛАЦЕНТ ЗДОРОВИХ ЖІНОК З ФІЗІОЛОГІЧНИМ ПЕРЕБІГОМ ВАГІТНОСТІ 27</p>	<p>Manasova G. S., Stasya Ya. A. Sitnikova V. A.. COMPARATIVE ANALYSIS OF THE HISTOPATHOLOGICAL FEATURES OF “POST-COVID” PLACENTAS AND PLACENTAS OF HEALTHY WOMEN WITH A PHYSIOLOGICAL COURSE OF PREGNANCY27</p>
<p>Абдуллаєва І. В., Валецький Ю. М. Калинчук С. В. ОСОБЛИВОСТІ СЕСТРИНСЬКОГО АМБУЛАТОРНОГО СПОСТЕРЕЖЕННЯ ЗА ХВОРИМИ НА ХРОНІЧНУ СЕРЦЕВО-СУДИННУ ПАТОЛОГІЮ З УРАХУВАННЯМ НАСЛІДКІВ ПАНДЕМІЇ КОВІД-19 ТА СТАНУ ХРОНІЧНОГО СТРЕСУ В УМОВАХ ВІЙНИ..... 37</p>	<p>Abdullaeva I. V., Valetskyi Yu. M. Kalinchuk S. V. FEATURES OF NURSING OUTPATIENT OBSERVATION OF PATIENTS WITH CHRONIC CARDIOVASCULAR PATHOLOGY TAKING INTO ACCOUNT THE CONSEQUENCES OF THE PANDEMIC COVID-19 AND THE STATE OF CHRONIC STRESS IN THE CONDITIONS OF WAR..... 37</p>