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PERINATAL ASPECTS OF MEDICAL CARE WITH COVID-19

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Purpose. *To determine perinatal aspects of medical care for COVID-19.* ***Materials and methods.*** *200 patients with confirmed SARS-CoV-2 hospitalized at the Kiev City Center for Reproductive and Perinatal Medicine were comprehensively examined: group 1 - 50 pregnant women with severe Covid-19 and group 2 - 150 pregnant women with moderate severity of the disease.* ***Research results.*** *Severe Covid-19 disease is observed in 12.2% of pregnant women, critical condition - in 7.5% of patients. Severe disease directly or indirectly determined a significantly higher incidence of pregnancy complications. First of all, this is placental insufficiency in the vast majority of patients (72.0%), which was manifested by fetal growth retardation and distress (in 32.0% and 48.0%). Half of the women experience oligohydramnios (50.0%), 38.0% have a threat of premature birth, and a third (30.0%) have premature birth. 44.0% of children are born in a state of asphyxia, 36.0% of children have manifestations of respiratory failure, and 16.0% have bilateral pneumonia. High incidence of neurological disorders (56.0%), gastrointestinal (50.0%), hypoglycemic (34.0%) and hemorrhagic (32.0%) syndromes. Testing of newborns for COVID-19 was positive in 6.0% of cases. 22.0% of children required intensive care unit care. Perinatal mortality was 0.4%.* ***Conclusions.*** *The identified high frequency of perinatal disorders in women with COVID-19 indicates the need for careful care for this category of pregnant women and their newborns, constant monitoring of vital functions, follow-up observation, and the development of clear algorithms for the actions of medical personnel depending on the patients' condition.*

Key words: *COVID-19, pregnancy, newborn, perinatal complications, perinatal care*

The coronavirus disease 2019 (COVID-19) pandemic has created significant challenges for healthcare delivery around the world. The novel coronavirus has meant a lack of knowledge and understanding of the nature of the infection, including a lack of data on the epidemiology, mechanisms of transmission, disease progression, and treatment options for people with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Much of the initial clinical recommendations were based on extrapolation of data and experience with other respiratory viruses. However, there was an understanding that the specifics of SARS-CoV-2 require a specific understanding of the pathophysiology and treatment approach [5]. Very quickly, from the beginning of 2020, studies began to be published, as clinicians were faced with the question of how to care for patients with COVID-19. There has been a significant surge in posts related to COVID-19. As of August 2023, more than 2 million publications about COVID-19 have been published [2].

During the early phase of the coronavirus disease 2019 (COVID-19) pandemic, pregnant women faced uncertain maternal and perinatal risks associated with SARS-CoV-2 [16].

According to published data, the prevalence of SARS-CoV-2 infection among pregnant women was 3-20% with a wide spectrum of severity, ranging from asymptomatic to extremely severe [6]. Most studies report that infection with COVID-19 during pregnancy is associated with a higher rate of preterm birth [10]. According to some studies, pregnant women with SARS-CoV-2 infection have a higher rate of preeclampsia [13], although this was not observed in a Canadian national study [10]. In addition, as already reported in early publications, among pregnant women, the severe form of COVID-19 is associated with gestational diabetes and fetal growth retardation compared to the mild form of COVID-19 [15].

The impact of SARS-CoV-2 on the outcome of pregnancy and the transmission of infection between mother and fetus remains an important question. Despite the fact that newborns diagnosed with COVID-19 were mostly asymptomatic or had a mild form of the disease, the impact of the disease in the early stages of pregnancy on its further course and consequences has not yet been investigated [11]. A systematic review of 47 studies showed that vertical transmission was confirmed in only 0.3% of patients, probable in 0.5%, and possible in 1.8% [7].

Current evidence suggests that severe acute respiratory syndrome caused by COVID-19 is associated with an increased frequency of perinatal disorders. Management of pregnant women with coronavirus disease 2019 (COVID-19) is similar to that of nonpregnant women, and effective treatment, including antiviral therapy, dexamethasone, and prophylactic anticoagulants, should not be withheld during pregnancy [8].

During the early period of the COVID-19 pandemic, management of pregnant women was often delayed until polymerase chain reaction (PCR) results were available, or even among those without symptoms. In view of the spread of the infection, a cesarean section was performed instead of a vaginal delivery to prevent transmission during delivery. In addition, if the mother's PCR test was positive, the separation of mother and child was practiced. At present, such recommendations have been revised. Most guidelines support placing newborns with an infected mother using a mask and maintaining hygiene, especially if the mother does not have fever or symptoms [1].

Most newborns of mothers infected with SARS-CoV-2 are not infected and are born in a satisfactory condition [9]. Neonatal morbidity (in particular, the need for artificial lung ventilation) is mostly associated with premature birth and adverse conditions of intrauterine development due to the critical illness of the mother due to COVID-19 [12, 14]. Neonatal adverse outcomes are thought to be the result of maternal hypoxia rather than direct exposure to the pathogen. Guan et al. [4] reported that fetal complications of COVID-19 include miscarriage (2%) and intrauterine growth retardation (10%). Lokken et al. [9] suggested that children born to mothers with severe or critical COVID-19 at the time of delivery are more likely to have a low birth weight (< 2500 g) and to be hospitalized in the neonatal intensive care unit for fetal indications.

Vaccination reduces the risk of progression of COVID-19 to a severe or critical form and the need for hospitalization of pregnant women [3].

To prepare for future pandemics, it is necessary to learn the lessons that this pandemic has provided to improve our preparation and response to new infections that may arise in the future. Policymakers and health leaders must identify effective and robust strategies to maintain safe maternal care even during global emergencies [8].

PURPOSE

To determine the perinatal aspects of medical care for COVID-19.

MATERIALS AND METHODS

200 patients with confirmed SARS-CoV-2 who were hospitalized at the Kyiv City Center for Reproductive and Perinatal Medicine (KNP «KMCRPM») were comprehensively examined: 1 group of 50 pregnant women with a severe course of Covid-19 who required intensive care in the anesthesiology department and intensive therapy and group 2 - 150 pregnant women with moderate severity, who were treated in the infectious-obstetrics department.

Pregnancy management and treatment were carried out in accordance with diagnostic and treatment protocols approved by the Ministry of Health of Ukraine.

The study was approved by the ethics committee of the P. L. Shupyk National Institute of Health of Ukraine, the work is a fragment of the NDR «Development of pregnancy management tactics after influenza and other acute respiratory viral infections». All studies were carried out after receiving the patient's informed consent for diagnosis and treatment.

All obtained data were processed by the methods of variational statistics accepted in medicine, using Fisher's angular transformation test and the Mann-Whitney test with a significance level of $p < 0.05$.

RESEARCH RESULTS AND THEIR DISCUSSION

In 2021 - 2023, 827 pregnant women with Covid-19 were hospitalized, 101 (12.2%) patients had a severe course, 41 (7.5%) women were in critical condition (Figs. 1, 2). The severity of the course of the disease and the number of hospitalizations depended on the strain of the virus. Thus, in the first half of 2021, when Alpha, Beta, Gamma symptoms were diagnosed, 84 patients were hospitalized, 9 (10.7%) of them had a severe course of the coronavirus, and 2 (2.4%) were in critical condition. The Delta strain turned out to be more contagious - in the second half of 2021, 234 pregnant women were hospitalized in 2021, this strain also had the most severe course: 78 (33.3%) patients were in serious condition, 39 (16.7%) were in critical condition . The Omicron strain is characterized by the highest contagiousness (214 hospitalized in 2 months of 2022, 427 patients per year) and the mildest course: only 14 (3.3%) pregnant women had a severe course, no critical conditions were observed. During the 10 months of 2023 (during this period, about 5 subspecies of

the Omicron strain were registered in Ukraine), 82 pregnant women were hospitalized, and the course of the disease was of moderate severity in all patients.

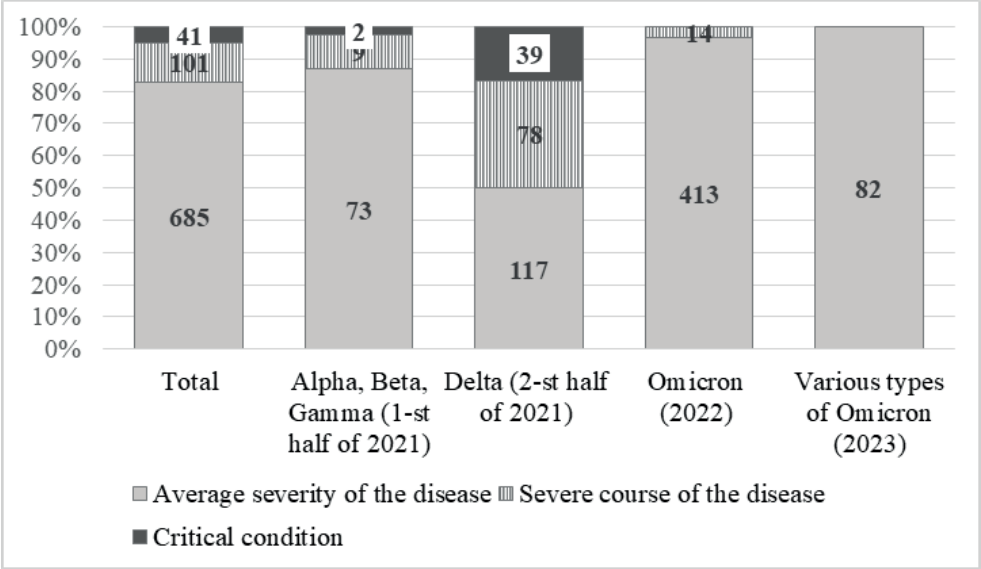

Figure 1 Structure of the severity of the course of the disease in pregnant women in the dynamics of the development of the pandemic Covid-19

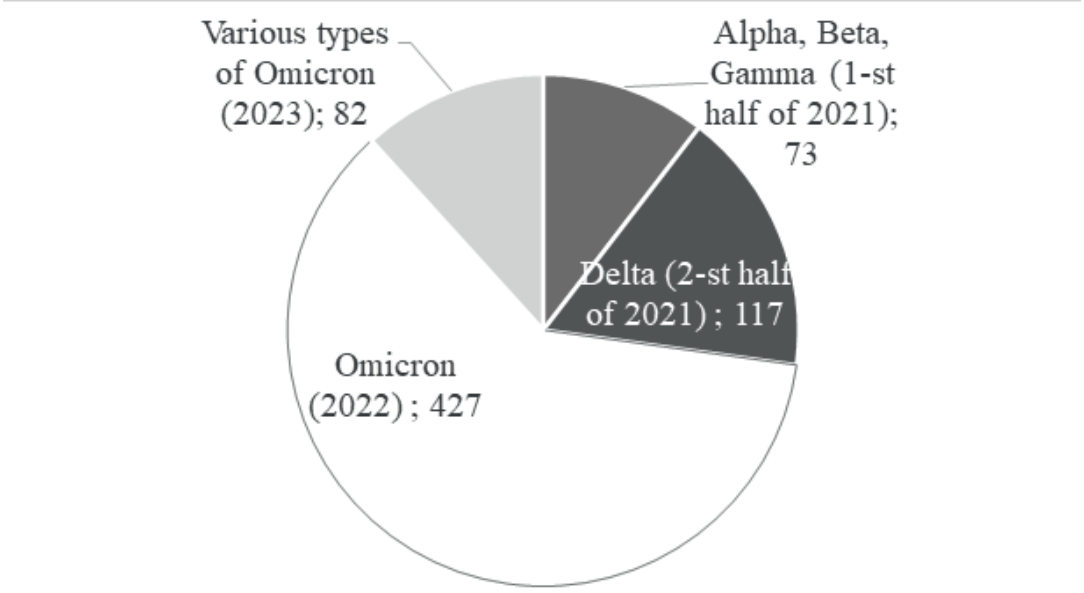

Figure 2 – Distribution of hospitalized pregnant women by strains Covid-19

The following features of the course of the disease for Covid-19 in the examined pregnant women were noted (Table 1). The body temperature rose to 38°C and above in half of the patients with a severe course (vs. 15.9% with a course of moderate severity, $p<0.05$). The duration of hyperthermia was on average 10.4 and 3.2 days by group. Pneumonia was diagnosed in all patients of group 1 and a third of patients in group 2 (31.0%). The average value of SpO2 saturation was 87.6±7.4% and 98.0±2.3% (minimum SpO2 62.8±14.3% and 93.4±4.1% $p<0.05$). Respiratory support was required by all patients of group 1 (average duration 12.4 days, from 3 to 41 days) using a concentrator, face mask or CPAP, and only 3 (2.0%) pregnant women with a mild course of the disease (from 2 to 5 days per hubs). Group 1 patients were hospitalized for an average of 16.8 ± 4.2 days (from 6 to 44) versus 6.8 ± 3.4 days in group 2 (from 1 to 18), the number of days in the ICU ranged from 2 to 26 (on average 7.7±3.4 days).

Table 1. Indicators of the course of the disease for Covid-19 in the examined pregnant women

Indicator	Group 1, n = 50		Group 2, n = 150	
	abs.n.	%	abs.n.	%
The body temperature rose to 38°C and above	26	52,0*	24	16,0
The duration of hyperthermia, days	10,4±3,1*		3,2±1,4	
Pneumonia	50	100,0	43	28,7
SpO2 average, %	87,6±7,4		98,0±2,3	
SpO2 minimum, %	62,8±14,3*		93,4±4,1	
Respiratory support	50	100,0	3	2,0
Average duration of respiratory support, days	11,7±4,2		2-5	
The duration of hospitalization, days	16,8 ±4,2*		6,8 ±3,4	

*Note. * - the difference is significant in relation to the indicator of women of group 2 (p<0.05).*

The course of the disease was characterized by the following changes in laboratory parameters (Table 2). Some women had thrombocytopenia: 22.0% and 6.7% in groups 1 and 2 ($p < 0.05$). At the time of hospitalization, leukocytosis was observed in 36.0% and 14.0% of patients ($p < 0.05$), the blood formula also changed: lymphopenia was noted in 88.0% and 52.0% of women, respectively ($p < 0.05$)). The addition of a bacterial infection was accompanied by a shift of the leukocyte formula to the left (the content of rod-nuclear leukocytes increased) in 86.0% and 50.0% of women of groups 1 and 2 ($p < 0.05$).

An increase in transaminases was observed: alanine aminotransferase (ALT) in 78.0% and 20.7% of women, respectively ($p < 0.05$), aspartate aminotransferase (AST) in 72.0% of patients in group 1 (against 31.3% in group 2, $p<0.05$), which may be associated with destructive changes in lung tissue.

Prothrombotic changes in the hemostasis system are indicated by a decrease in PF in 62.0% and 32.7% of patients, which is confirmed by an increased level of D-dimer in 80.0% of women of group 1, in some cases (in 9.5% of women) the value of the indicator reached 15,000 ng/ml, and in 54.0% of women of group 2 (an increase above 10,000 ng/ml in one case – 0.01%).

The increase in markers of inflammation in patients of group 1 is a reflection of the destructive effect of inflammatory processes in Covid-19. Thus, C-reactive protein exceeded normative values in all patients of group 1 and 60.7% of patients in group 2, and in 48.0% of cases its level was higher than 50 mg/l (versus 15.3% in group 2, $p< 0.05$). The level of interleukin-6 is higher than normal in all women in group 1 and 20.0% of group 2, and its concentration exceeded 20 mg/ml in 54.0% and 9.3% of women, respectively ($p<0.05$). An increased content of procalcitonin was registered in 66.0% of patients of group 1, which is 11 times more than the corresponding frequency in group 2 (6.0%, $p<0.05$), while in 24.0% of women of group 1 this increase was significant (above 0.5 ng/ml).

As is known from the data of scientific publications, older age and the presence of somatic pathology (cardiovascular, endocrine, and others) can be attributed to the risk factors of a severe course of SARS-CoV-2. According to our data (Table 3), a third of patients in group 1 were over 35 years old (36.0%), which is almost 3 times more than in group 2 (12.7%). The somatic anamnesis was complicated in 16 (32.0%) and 14 (10.6%) patients of groups 1 and 2, respectively, thyroid pathology stood out among the diseases (18.0% and 6.0%, $p<0.05$) and cardiovascular disorders (20.0% and 4.7%, $p<0.05$). The vast majority of women in group 1 were obese or overweight (78.0% versus 48.7% in group 2, $p<0.05$), and almost a third had III-IV degree obesity (28.0% against 4.0%; $p<0.05$).

Table 2. Changes in laboratory indicators in pregnant women, patients with COVID-19

Indicator	Group 1, n = 50		Group 2, n = 150	
	abs.n.	%	abs.n.	%
Thrombocytopenia	11	22,0*	10	6,7
Leukocytosis	18	36,0*	21	14,0
Lymphopenia	44	88,0*	78	52,0
Increase of the content of rod-shaped leukocytes	43	86,0*	75	50,0
Increase of ALT	39	78,0*	31	20,7
Increase of AST	36	72,0*	47	31,3
Decrease of PT	31	62,0*	49	32,7
Increase of D-dimer	40	80,0*	81	54,0
Increase CRP (above 50 mg/l)	24	48,0*	23	15,3
Increase of interleukin-6 (above 20 pg/ml)	27	54,0*	14	9,3
Increase of procalcitonin (above 0,1 ng/ml)	33	66,0*	9	6,0

Note. * - the difference is significant in relation to the indicator of women of group 2 ($p<0.05$).

Table 3. Medico-social risk factors for a severe course of the disease due to Covid-19 in examined pregnant women

Indicator	Group 1, n = 50		Group 2, n = 150	
	abs.n.	%	abs.n.	%
Age over 35 years	18	36,0*	19	12,7
Pathology of the thyroid gland	9	18,0*	9	6,0
Cardiovascular pathology	10	20,0*	7	4,7
Obesity	34	78,0*	73	48,7
in particular, III - IV degrees	14	28,0*	6	4,0

Note. * - the difference is significant in relation to the indicator of women of group 2 ($p<0.05$).

The severe course of COVID-19 is accompanied by an increase in the frequency of obstetric and perinatal complications (Table 4). Signs of placental dysfunction were observed in most women of group 1 (72.0% vs. 34.0% in group 2; $p<0.05$), which caused fetal distress in half of pregnant women (48.0% vs. 17.4%; $p < 0.05$) and fetal growth retardation in a third of women (35.7% vs. 10.9%; $p<0.05$). Anemia in pregnant women was noted in 56.0% versus 26.0%, respectively ($p<0.05$). Attention is drawn to the high frequency of oligohydramnios (50.0% versus 20.0%; $p<0.05$), in 14.3% - ahydramnios (versus 1.3%). Preeclampsia was observed 2.5 times more often than in group 2 (12.0% vs. 4.7%; $p<0.05$). A third of patients gave birth prematurely (30.0% vs. 15.3%), among them 6 (12.0%) gave birth before 32 weeks. Delivery by caesarean section was performed in 54.0% versus 31.3% of patient groups, respectively.

Pathohistological examination of the placenta of patients with COVID-19 confirmed placental dysfunction, which was manifested by signs of chorioamnionitis in 9 (18.0%) samples of women of group 1 and in 7 (4.7%; $p<0.05$) of group 2, which is associated with intrauterine infection. Macroscopically, thromboses of blood vessels of the placenta and umbilical cord were detected.

Table 4. Complications of pregnancy and childbirth in women with COVID-19

Indicator	Group 1, n = 50		Group 2, n = 150	
	abs.n.	%	abs.n.	%
Placental dysfunction	36	72,0*	51	34,0
Fetal growth retardation	16	32,0*	15	10,0
Fetal distress	24	48,0*	26	17,3
Anemia	28	56,0*	39	26,0
Oligohydramnios	25	50,0*	30	20,0
Ahydramnios	7	14,0*	2	1,3
The threat of premature birth	19	38,0*	24	16,0
Preeclampsia	6	12,0*	7	4,7
Premature rupture of the fetal membranes	8	16,0*	11	7,3
Premature birth	15	30,0*	23	15,3
Caesarean section	27	54,0*	47	31,3

Note. * - the difference is significant in relation to the indicator of women of group 2 ($p<0.05$).

The microscopic picture of the placenta was characterized by the presence of foci of hemorrhage and focal necrosis, leukocyte infiltration. Widespread areas with villi sealed with fibrinoid were noted. The amount of fibrinoid is also increased in the intervillous space. Diffuse deciduitis, hemorrhages, and focal heart attacks were noted. Such pathological changes can cause premature rupture of fetal membranes and premature birth, which negatively affects the condition of newborns. Such placental abnormalities often cause negative consequences for the nervous system of newborns regardless of etiological reasons, therefore children born to women whose pregnancy was complicated by SARS-CoV-2 infection require long-term observation to monitor the body's condition.

According to Table 5, 44.0% of children whose mothers suffered from a severe form of coronavirus infection were born asphyxiated (versus 15.3% in group 2; $p<0.05$), and in 16.0% of cases it was severe asphyxia, which was several times higher than the corresponding frequency in group 2 (2.2%). A third of children were born prematurely (30.0% vs. 15.3%, $p<0.05$), 34.0% vs. 16.7% - with signs of hypotrophy ($p<0.05$).

Table 5. Condition of newborns in women with COVID-19

Indicator	Group 1, n = 50		Group 2, n = 150	
	abs.n.	%	abs.n.	%
Asphyxia at birth	22	44,0*	23	15,3
particularly severe	8	16,0*	4	2,7
Prematurity	15	30,0*	23	15,3
Hypotrophy	17	34,0*	25	16,7

Note. * - the difference is significant in relation to the indicator of women of group 2 ($p<0.05$).

Newborns tested positive for COVID-19 in 3 (6.0%) cases in group 1 and 2 (1.3%) in group 2.

In 36.0% of children of group 1, manifestations of respiratory insufficiency were observed (against 12.7% of newborns of group 2; $p<0.05$), in 9 (19.0%) cases, severe respiratory distress syndrome accompanied by shortness of breath was diagnosed. due to cyanosis of the skin, a decrease in saturation to 86%, unstable hemodynamics, these children needed respiratory support (artificial lung ventilation). Mild and moderate respiratory failure was diagnosed in 10.0% and 2.7% of group 2 newborns.

8 (16.0%) children of group 1 were diagnosed with radiologically confirmed bilateral pneumonia. At the same time, they have marked leukocytosis (up to 40x106/ml), an increase in erythrocytes (up to 22%), thrombocytopenia (up to 80x106/ml), anemia (hemoglobin level below 90 g/l), an increase in inflammatory markers: levels of C-reactive protein (over 1 mg/l) and procalcitonin (from 0.5 ng/ml to 2.0 ng/ml), low protein level (up to 45 g/l). A shift in hemostasis towards increased coagulation potential was noted (shortening of activated partial thromboplastin time below 40 s and prothrombin time below 10 s, appearance of fibrin degradation products). Clinical manifestations of hemorrhagic syndrome were detected from the second day (petechiae, gastrointestinal bleeding), on the fifth day - ulcerative-necrotic enterocolitis of varying degrees of severity. Against the background of multiple organ failure, two children died (mortality was 0.4 ‰).

In addition to respiratory distress syndrome and hemorrhagic syndrome, a high frequency of other disorders of the period of early neonatal adaptation was observed (Figure 3).

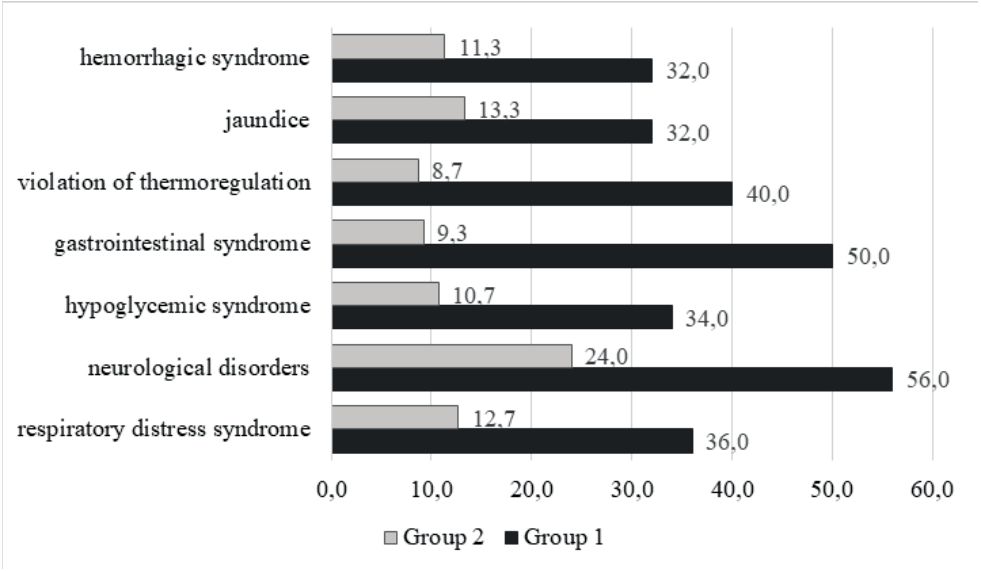

Figure 3 – Frequency of maladjustment syndromes in newborns from mothers whose pregnancy was complicated by the disease due to COVID-19

Attention is drawn to the high frequency of neurological disorders, which were noted in more than half of the children in group 1 (56.0% vs. 24.9%; $p<0.05$), mainly in the form of depression syndrome. Half of the children had gastrointestinal syndrome (50.0% vs. 9.3%; $p<0.05$), thermoregulation disorders were observed in 40.0% of children (versus 8.7%; $p<0.05$), in 34, 0% hypoglycemic syndrome (versus 10.7%; $p<0.05$).

The vast majority of children were breastfed, which was canceled only in cases caused by the serious condition of the mother or the child.

22.0% of children in group 1 needed care in the intensive care unit (versus 4.7% of children in group 2, $p<0.05$).

CONCLUSION

In the dynamics of the COVID-19 pandemic, both the frequency of morbidity during pregnancy and the severity of its manifestations changed with the change of virus strains. The most severe course of the disease, as in non-pregnant women, was caused by the Delta strain. The Omicron strain at the beginning (2022) was characterized by the highest contagiousness and the lightest course. In 2023, various strains of Omicron prevail, there is a tendency to decrease the frequency and severity of the disease, which gave the WHO reason to cancel the pandemic status in May 2023, but the virus remains and continues to kill, there is also a risk of the appearance of completely new viruses unknown to mankind, which determines the need to study the experience of combating COVID-19, in particular in the field of perinatology, in order to develop a general strategy for actions in the event of mass infectious outbreaks in the conditions of a new reality.

A severe course of the disease due to Covid-19 is noted in 12.2% of pregnant women, critical condition - in 7.5% of patients. The severe course of the disease was manifested by pneumonia, prolonged hyperthermia, and a

decrease in saturation. Laboratory changes include thrombocytopenia, leukocytosis, lymphopenia, increased transaminases, and D-dimer. The increase in markers of inflammation (C-reactive protein, interleukin-6, procalcitonin) is a reflection of the destructive effect of inflammatory processes in Covid-19.

Medical and social risk factors for severe disease in pregnant women include age over 35 years, thyroid pathology, cardiovascular disorders, III-IV degree obesity.

The severe course of the disease directly or indirectly caused a significantly higher frequency of pregnancy complications. First of all, it is placental insufficiency in the vast majority of patients (72.0%), which caused fetal growth retardation and fetal distress (in 32.0% and 48.0%). Half of the women have low water (50.0%), 38.0% are at risk of premature birth, and a third (30.0%) are premature birth. 44.0% of children are born asphyxiated, 36.0% of children have respiratory failure, and 16.0% have bilateral pneumonia. High frequency of neurological disorders (56.0%), gastrointestinal (50.0%), hypoglycemic (34.0%) and hemorrhagic (32.0%) syndromes Testing of newborns for COVID-19 gave a positive result in 6.0% of cases . 22.0% of children needed care in the intensive care unit. Perinatal mortality was 0.4 ‰.

The revealed high frequency of perinatal disorders in women with COVID-19 indicates the need for careful care of this category of pregnant women and their newborns, constant monitoring of vital functions, catamnetic care, development of clear algorithms for the actions of medical personnel depending on the condition of the patients.

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РЕЗЮМЕ

ПЕРИНАТАЛЬНІ АСПЕКТИ МЕДИЧНОЇ ДОПОМОГИ ПРИ COVID-19

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Мета дослідження. Визначити перинатальні аспекти медичної допомоги при COVID-19. **Матеріал і методи дослідження.** Комплексно обстежено 200 пацієнток з підтвердженим SARS-CoV-2, що були госпіталізовані в КНП «Київський міський центр репродуктивної та перинатальної медицини»: 1 група – 50 вагітних з тяжким перебігом Covid-19 та 2 група – 150 вагітних з середньою тяжкістю. **Результати дослідження.** Тяжкий перебіг захворювання на Covid-19 відмічається у 12,2 % вагітних жінок, критичний стан - у 7,5 % пацієнток. Тяжкий перебіг захворювання прямо чи опосередковано обумовлював суттєво вищу частоту ускладнень вагітності. Перш за все, це плацентарна недостатність у переважної більшості пацієнток (72,0 %), що проявлялось затримкою росту плода та його дистресом (у 32,0 % та 48,0 %). У половини жінок спостерігається маловоддя (50,0 %), у 38,0 % - загроза передчасних пологів, у третини (30,0 %) – передчасні пологи. 44,0 % дітей народжуються в стані асфіксії, у 36,0% дітей - прояви дихальної недостатності, у 16,0 % - двобічна пневмонія. Висока частота неврологічних порушень (56,0 %), гастроінтестиніального (50,0 %), гіпоглікемічного (34,0 %) та геморагічного (32,0 %) синдромів Тестування новонароджених на COVID-19 дало позитивний результат у 6,0 % випадків. 22,0 % дітей потребували догляду у відділенні інтенсивної терапії. Перинатальна смертність склала 0,4 ‰. **Висновки.** Виявлена висока частота перинатальних порушень при захворюванні жінки на COVID-19 вказує на необхідність ретельного догляду за цією категорією вагітних та їх новонароджених, постійного моніторингу життєво важливих функцій, катамнестичного догляду, розробки чітких алгоритмів дій медичного персоналу залежно від стану пацієнтів.

Ключові слова: COVID-19, вагітність, новонароджений, перинатальні ускладнення, перинатальний догляд