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Monograph

RESPIRATORY VIRAL INFECTIONS IN PREGNANT WOMEN: IMPACT ON THE MOTHER-PLACENTA-FETUS SYSTEM

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The monograph summarizes clinical and laboratory indicators of the course of respiratory viral infections in pregnant women. The results of scientific and practical research, as well as our own clinical, instrumental and functional observations performed on a large contingent of pregnant women with respiratory viral infection are presented. Issues of etiology, pathogenesis, anamnesis, complex diagnostics, prognosis and prevention were discussed. Methods for predicting and preventing possible complications in pregnancy, childbirth and the postpartum period in women who have had respiratory viral infections in different trimesters of pregnancy are summarized and recommended; a number of diagnostic and clinical examples from our own observations are given.

The publication is intended for obstetrician-gynecologists and doctors of related specialties.

The monograph was approved at a meeting of the Academic Council of Samarkand State Medical University.

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CONTENT

ABBREVIATIONS

ALT – alanine aminotransferase

AST – aspartate aminotransferase

AT III – antithrombin III

APTT – activated partial thromboplastin time

ACE2 – angiotensin-converting enzyme

BPS – biparietal size

WHO – World Health Organization

FL – femur length

DIC – disseminated intravascular coagulation

CT – computed tomography

LUA – left uterine artery

INR – international normalized ratio

UP – undeveloped pregnancy

FAC – fetal abdominal circumference

RT-PCR – reverse transcription polymerase chain reaction

PI – placental insufficiency

PTT – prothrombin time

PTI – prothrombin index

RI – resistance index

PI – pulsation index

SDR – systolic-diastolic ratio

FGRS – fetal growth restriction syndrome

TBUCA – terminal branches of the umbilical cord artery

CNS – central nervous system

SARS-CoV-2 – Severe acute respiratory syndrome-related coronavirus 2

INTRODUCTION

Respiratory viral infections in the process of human civilization have manifested themselves through various viral infections. In the 21st century in the history of mankind, COVID-19 became a global problem, and its causative agent was the SARs-CoV-2 virus and was the cause of a pandemic around the world, and today this virus has turned into a seasonally worsening respiratory viral infection. This virus can also cause serious health problems during pregnancy. Unlike the general population, pregnant women constitute a special group with a significantly higher risk of viral infection as a unique “immunological” condition and changes in the function of all organs and systems during pregnancy; in this regard, the study of the functional state of the mother-placenta-fetus system in pregnant women who have had viral infections remains a modern requirement from a scientific and practical point of view.

Large-scale studies are being conducted all over the world aimed at studying the effect of respiratory viral infections on the state of hemodynamics in the “mother-placenta-fetus” system in pregnant women. In this regard, the priority direction of scientific research remains the study of the function of the vessels of the uteroplacental complex, the state of the vascular endothelium, the hemostasis system and the morphology of the placenta in pregnant women with respiratory viral infections in the first, second and third trimesters of pregnancy, with particular importance being given to improving the tactics of managing pregnancy and childbirth in women.

CHAPTER I. RESPIRATORY VIRAL INFECTION: IMPACT ON THE COURSE OF PREGNANCY AND THE MOTHER-PLACENTA-FETUS SYSTEM (LITERATURE REVIEW)

1.1. Respiratory viral infections. Infectious process clinic

At the end of 2019, a new type of respiratory virus was discovered and identified as, causing a cluster of pneumonia cases in Wuhan, Hubei Province, China. The virus spread quickly, causing an epidemic throughout China, followed by a sharp increase in cases in other countries around the world. In February 2020, WHO designated this disease as COVID-19, i.e. coronavirus disease 2019 [63]. The virus that causes COVID-19 is designated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); it was previously called 2019-nCoV [59; p.100-107].

More often, pregnant women may develop severe pneumonia, as a result of which 22–30% of them are admitted to the intensive care unit, and in 15–26% of cases it may progress to respiratory distress syndrome. Among hospitalized pregnant women, the mortality rate is 4–15%. The overall case fatality rate is 1%.

The incubation period ranges from 2 to 14 days, with an average of 5-7 days. The spectrum of clinical symptoms in the general population varies from a mild course of the disease to the development of critical conditions. In most cases, severe disease does not develop [51; p.100-118, 54; p.100-104].

According to the CDC (Centers for Disease Control), the spectrum of disease severity is presented as, a result of an analysis of the course of the disease in 44,500 patients in the PRC (People's Republic of Korea) [65; p.1708-1720.]:

- the absence of pneumonia or its mild course was recorded in 81% of patients;
- severe illness (development of shortness of breath, hypoxia, damage to more than 50% of the lung tissue according to the results of imaging tests) was noted in 14%;

- critical conditions with the development of respiratory failure, shock, multiple organ failure were observed in 5% of patients;
- The average mortality rate was 2.3%, with no deaths observed among patients who were not critically ill.

The mortality rate ranged from 5.8% in Wuhan to 0.7% in the rest of China [68; p.497-506].

Clinical course. The most common serious clinical manifestation of respiratory viral infection in the general population is pneumonia, characterized primarily by fever, cough, shortness of breath, and the appearance of bilateral infiltrates in the lungs. There are no specific clinical manifestations that could help distinguish COVID-19 from other viral respiratory infections.

An analysis of the clinical manifestations of respiratory viral infections in 138 patients in Wuhan showed that the most common symptoms at the time of manifestation were [68; pp. 497-506]: fever in 99% of cases; weakness – in 70% of patients; dry cough - 59%; lack of appetite – 40%; myalgia - in 35%; sputum production - 27%; other, less common symptoms include headache, sore throat and rhinorrhea. Some patients, in addition to respiratory symptoms, may complain of gastrointestinal disorders (for example, nausea and diarrhea) [58]. In some cases, symptoms include confusion (9%), headaches (8%), hemoptysis (5%), palpitations [45; p.501-503].

There are also cases of asymptomatic disease, but the frequency of this variant remains unclear [39; p.167-169].

Just like patients in the general population, most pregnant women present with complaints similar to symptoms of a cold or flu of mild or moderate severity. It should be remembered that pregnant women are prone to developing more severe forms of viral infection, complicated by severe pneumonia and hypoxia. Although it is known that such forms of seasonal viral infection are typical for older people, people with immunodeficiency conditions, suffering from chronic diseases, such as diabetes, cancer, lung diseases, should be wary of pregnant women. Although the

absolute risk for pregnant women is negligible, symptoms of severe disease in pregnant women must be identified and appropriate therapy provided without delay [35; p.35-40].

The diagnosis is made on the basis of clinical manifestations, including fever, general weakness, myalgia, dry cough, and a feeling of shortness of breath. In some cases, nasal congestion, runny nose, sore throat, hemoptysis, and diarrhea may be present. In a general blood test in the early stages of the disease, the number of leukocytes may be normal or reduced, and lymphopenia may be observed. C-reactive protein levels are elevated. Some patients develop thrombocytopenia, increased levels of liver enzymes and creatine phosphokinase [43; p.310-318].

To confirm or exclude viral pneumonia, one of the most valuable instrumental diagnostic methods is computed tomography (CT) of the chest without contrast. Investigation should be carried out in all suspected cases, given that the risk to the fetus is negligible. It has been proven that the sensitivity of CT in diagnosing covid-19 is higher than the PCR method (98% compared to 71%) [25; p.262-265]. Radiological evidence of viral pneumonia is present in the vast majority of cases of seasonal respiratory viruses in pregnant women. The main manifestations of pneumonia are ground glass infiltrates.

For laboratory diagnosis of respiratory viruses, the PCR method is used. The main material for laboratory research methods was a smear from the nasal and/or oropharynx [40; p.34-36, 44; p.653-658].

Thus, the clinical course of respiratory viral infections during pregnancy is no different from non-pregnant women and is characterized by increased body temperature, cough with difficult sputum, chest pain, and sometimes - diarrhea. In the general blood test, lymphopenia and an increase in CRP, AST, ALT, and LDH levels are observed. Radiation diagnostic methods reveal one- or two-sided foci of infiltration of the “frosted” glass type, which also does not differ from non-pregnant women.

1.2. The impact of respiratory viral infections on pregnancy and fetus

Pregnancy is a physiological condition in which predisposition to respiratory viral infections. Due to physiological changes in the immune and cardiopulmonary systems, pregnant women increase the likelihood of severe respiratory disease viral infections. There is currently no evidence that pregnant women are more susceptible to infection than the general population, although there is concern that due to changes in the immune response in pregnant women, the likelihood of developing a more severe clinical picture increases.

In epidemics caused by the A(H1N1)09 virus in 2009-2010, infection of pregnant women with swine flu amounted to 28% [53; p.288-295]. The fatal outcome due to infection with the SARS-CoV virus in pregnant women reached 25% [54; p.100-104]. It was also noted that viruses such as SARS-CoV and MERS-CoV in pregnant women led to severe complications of pregnancy, as a result of which the need for artificial ventilation and hospitalization in the intensive care unit increased, among which kidney failure and death were often observed.

Similar opinions are put forward by WHO experts and Royal Society of Obstetricians and Gynecologists (Royal College of Obstetricians and Gynecologists, UK) (2020) - in pregnant women women are at greater risk of contracting SARS-CoV-2 due to changes in the body, especially in the cardiopulmonary and immune systems. But there is also supporting evidence that Covid-19 has pregnant women do not have a more severe course than adults in the general population [59; p.100-107].

Risk factors for severe respiratory viral infections among pregnant women, there are such somatic diseases as chronic diseases of the respiratory system (bronchial asthma of varying degrees severity), diseases of the cardiovascular system (hypertension, diabetes mellitus), immunosuppressive conditions (oncological diseases), as well as obesity (BMI>40), kidney and liver diseases [52; p.809-815].

Obstetric complications due to seasonal respiratory viral infections among pregnant women may include spontaneous miscarriages (up to 2-3%), fetal growth restriction syndrome (10-14%), premature birth (25-40%), and also due to infection with viruses during pregnancy and the development of severe pneumonia, an increase in the percentage of abdominal births was observed due to the development of such complications as inconclusive fetal condition [40; p.46-47, 52; p.809-815].

There is currently no evidence that pregnant women with seasonal respiratory viral infections have an increased risk of spontaneous early miscarriage and failure to progress to pregnancy. There is also no convincing connection between coronavirus infection and an increased risk of pregnancy loss in the second trimester. A case of infection of a fetus from a mother with Covid-19 has been published, and therefore vertical transmission is also considered probable [37; p.152-156]. It is currently considered unlikely that the virus has any effect on fetal development. There is also no evidence that the virus exhibits teratogenic properties [46; p.861-865].

Although some publications contain reports of cases of preterm birth in women with viral infections, it is not clear which part can be classified as iatrogenic and which part can be classified as spontaneous preterm birth. It is known that iatrogenic delivery was carried out in connection with indications from the mother associated with a viral infection [32; p.115-118].

Some reports spoke of the development of intrauterine fetal suffering, premature prenatal rupture of membranes [28; p.26-27].

Thus, pregnancy itself and the resulting conditions and physiological changes in the female body create a predisposition to infection and a more severe course of respiratory viral infections. And various somatic diseases existing in the body of pregnant women further aggravate the course of respiratory viral infections and can lead to the development of various complications of pregnancy.

1.3. The hemostasis system in pregnant women with respiratory viral infections

Severe forms of respiratory viral infections are associated with coagulation changes, mainly characterized by increased levels of D-dimer and fibrinogen, with a higher risk of thrombosis, especially pulmonary embolism. “Intravascular blood coagulation during Covid-19 determines the entire course of the disease,” this is how Academician A.D., a leading obstetrician-gynecologist in the field of hemostasiology, titled his interview dated June 5, 2020. Makatsaria [24]. Although Covid-19 primarily causes a lower respiratory tract infection, manifesting as cough, fever, shortness of breath and lethargy, it can also have cardiovascular and immune system complications such as mono- or multiorgan failure and disseminated intravascular coagulation (DIC) [41; p.373-381]. There is limited data on the effect of the virus on the coagulation potential of pregnant women, including women infected with other strains of coronavirus - severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) [6; p.61-65, 15; p.89-94]. Disruption of Virchow's triad due to COVID-19 and normal physiological changes during pregnancy place women at great risk for arterial, venous, and placental thrombi, which can be controlled with antithrombotic pharmacologic agents, including antiviral and anti-inflammatory drugs.

Natural physiological changes during pregnancy themselves cause a hypercoagulable state. This is manifested, firstly, by increased levels of coagulation factors (factors VII, VIII and X; von Willebrand factor (vWF); D-dimer; C-reactive protein; and fibrinogen). At the same time, the number of inhibitors of the fibrinolysis system increases. There is also a moderate prolongation of prothrombin time (PT) and/or activated partial thromboplastin time (APTT), decreased protein C levels and resistance to activated protein C, which increases especially in the second and third trimesters, and therefore these factors cannot inhibit coagulation. The anatomical changes occurring in the pregnant woman’s body also play an important role due to compression of the pelvic veins by the pregnant uterus, which leads to

decreased blood circulation in the lower extremities. This leads to stagnation, which can contribute to the formation of a blood clot - thrombus [6; pp.61-65, 36; pp.34-36]. Therefore, all hospitalized patients with seasonal respiratory viral infections are strongly advised to monitor platelet counts, PT and/or aPTT, D-dimer and fibrinogen levels.

Invasion of endothelial cells by the virus leads to endothelial cell damage and impaired fibrinolytic function, which promotes thrombus formation and large release of vWF. Loss of protective endothelial function leads to suppression of the clot lysis system, which worsens the hypercoagulable state. In respiratory viruses, an increase in intravascular fibrin deposition has also been found, which leads to increased blood viscosity and slower circulation. All these data confirm the fact that seasonal viruses are a risk factor for the formation of blood clots and the development of thromboembolism [4; p.39-43, 7; p.126-129]. It has been established that during viral infections, neutrophilia, leukocytosis, an increase in PT, an increase in interleukins: IL-6 and IL-8, as well as an increase in D-dimers are observed. The neutrophil-to-lymphocyte ratio (NLR) is a prognostic factor for critical disease (low risk NLR <3.13 and high risk ≥3.13) [23; p.1421-1428, 41; p.373-381]. Coagulopathy associated with coronavirus infection in the initial stages of the disease is characterized by the development of hypercoagulation without signs of DIC syndrome. There is an increase in D-dimer, a moderate decrease in the number of platelets (the number of platelets <150*109 /l is found in 70 - 95% of patients), a slight prolongation of PT, an increase in fibrinogen ("acute phase protein of inflammation"). In this case, the concentration of antithrombin III decreases to 80%, and the concentration of protein C does not change much [5; p.31-34, 34; p.57-67].

Coagulopathy during coronavirus infection does not have typical signs of consumption of fibrin and platelet degradation products. There is also no microangiopathy [12; p.235-237, 14; p.110-113]. In connection with the above, monitoring of D-dimer, platelet and fibrinogen counts, as well as PT can become prognostic criteria for hospitalized patients with coronavirus infection [11; p.645-657]. To identify hemostasis disorders and an increase in the risk of thrombosis (the

frequency of VTEC in patients with coronavirus infection ranges from 27 to 69% [66; p.134-145] or hemorrhagic complications, as well as the development of thrombophilia of the microcirculatory circulation and multiple organ failure, it is important to monitor indicators such as D-dimer, fibrinogen, platelet count, PT, ESR, C-reactive protein, lactate dehydrogenase, triglycerides, ferritin [8; p.214-225].

If a severe infection occurs, then secondary activation of blood coagulation occurs and it does not cope with the endogenous mechanisms of the anticoagulation system, and an acute generalized inflammatory reaction leads to extensive damage to the vascular endothelium, which can result in acute disseminated intravascular coagulation syndrome, hypoxia, tissue ischemia, dysfunction of vital organs, which leads to multiple organ failure [11; p.645-657]. In surviving patients with coronavirus infection, disseminated intravascular coagulation syndrome was recorded in only 0.6% of cases, while in those who died, this syndrome was recorded in 71.4% of cases. V. Bitsadze et al., (2020). established the pathogenesis of DIC syndrome during coronavirus infection [8; p.214-225, 10; p.235-238]. These are three interrelated processes: the cytopathic damaging effect of the virus on the vascular endothelium, a “cytokine storm” with the release of von Willebrand factor, which stimulates the activation of both the external and internal blood coagulation pathways, and the development of systemic vasculitis with damage to small vessels [33; p.71-94]. The main and available therapy for this condition is treatment with low molecular weight heparins.

1.4. The mother-placenta-fetus system and the influence of respiratory viral infections on it

Numerous studies on the effect of respiratory viruses on the human body have shown that this infection selectively affects the vascular endothelium, causing vasculitis in many organs and systems [43; p.310-318, 50; p.2198-2200,]. From this evidence comes the assumption that systemic damage to the vascular endothelium can lead to disruption of placental formation, the development of placental oxidative

stress and a variety of pregnancy complications associated with this [1; pp.12-14, 17; p.380-384].

Many early reports of respiratory viral infections during pregnancy recommended cesarean section, isolation of the newborn from the mother at birth, and bottle feeding. Reasons included previous experience of the severity of coronavirus infections during pregnancy, as well as the intention to protect the newborn from infection. [46; p.861-865].

To date, 28 cases have been published in which the possibility of vertical transmission of SARS-CoV 2 has been confirmed. To confirm accurate vertical transmission, detection of the virus by PCR has been proposed, in either cord or neonatal blood collected within the first 12 hours after birth, or amniotic fluid collected before rupture of membranes is required [29; pp.185-188, 42; p.6-15]. None of the cases reported to date have met these criteria, although some have reported negative test results. A few cases deserve special attention: 9 cases report a positive nasopharyngeal swab in a newborn on the day of birth. The authors did not describe procedures or measures to clean the infant's oropharynx, mouth, nostrils, or face before swab collection, suggesting that the presence of the virus may be associated with infection of the infant during delivery through the mother's feces. When the smear was taken again, the virus was not detected, and the baby remained healthy [16; pp.56-59, 39; pp.167-169].

The UKOSS (UK Obstetric Surveillance System) studies reported 12 of 24 cases of possible vertical transmission. Limited information was provided for 12 newborns, but 6 of the 12 infants tested positive for Covid-19 within 12 hours of birth. But it is unknown what test method was used and whether it was a nasopharyngeal swab without the precaution of washing the infant before testing, again may be the result of contamination. In one case, there was a positive nasopharyngeal swab of a newborn on the day of birth after carefully separating the baby and cleaning the baby before taking the swab. [56; p.100-101]. For cases where the mother is suspected or confirmed to have Covid-19 and the baby does not require neonatal care, guidelines, including those in the UK and Canada, recommend skin-

to-skin contact and breastfeeding if the mother follows hand hygiene precautions and wears a surgical face mask [47; p.17-22]. UNICEF guidelines strongly recommend breastfeeding for all children, including premature and sick children. It is also recommended to maintain a physical distance of more than two meters from each other [20; pp.86-89]. The low rates of neonatal infection after cesarean section are consistent with the earliest report of Covid-19 in pregnancy. It has been established that respiratory viral infections should not be an indication for cesarean section, artificial feeding, or isolation of the infant from the mother. Caesarean section should be performed only for obstetric indications [3; pp.11-13, 13; pp.51-53]. Mothers who are breastfeeding and sharing a room with their infants should continue to monitor for viral infection, maintain hygiene precautions, and wear a waterproof surgical face mask, if available, while feeding or caring for the infant. There is no evidence that separating the baby from the mother is beneficial if precautions are taken and cohabitation and breastfeeding are encouraged. Isolation should only be performed if clinically necessary. Neonatal viral infection is rare, with atypical symptoms, and the rate of infection is not higher, when the child is born vaginally, is breastfed, or is allowed contact with the mother [27; p.52-56].

The likelihood of SARS-CoV-2 infection through amniotic fluid during the Covid-19 pandemic is unlikely [29; p.185-188]. Unfortunately, this evidence was based, on samples collected during the early stages of the Covid-19 outbreak [64; p.272-274]. One study reported a positive test for SARS-CoV-2 infection in the amniotic fluid of a pregnant woman [63; p.112-113]. Due to the poor health of the pregnant woman, a cesarean section was performed in this case, and the premature newborn was born at 33 weeks of gestation. This newborn was positive for SARS-CoV-2, but without signs of respiratory failure. He was bottle-fed. Due to respiratory complications, the mother died 16 days after cesarean section. Viral RNA was determined in amniotic fluid samples using reverse transcription PCR (RT-PCR) among pregnant women with a positive result and who had previously suffered coronavirus diseases [18; pp. 109-182]. Results from studies evaluating amniotic fluid have suggested that transmission of SARS-CoV-2 through amniotic fluid is

unlikely. Only one study reported SARS-CoV-2 positivity in amniotic fluid. This case was likely related to contamination of the amniotic fluid sample. Ten studies evaluating cord blood samples showed negative results for SARS-CoV-2 [49; p.561-567]. These data support the results of some studies that found no evidence of SARS or MERS viral shedding in umbilical cord blood. One study tested positive for SARS-CoV-2 in the umbilical cord stump of a newborn who tested positive for SARS-CoV-2. The same study reported positivity for SARS-CoV-2 in the placenta. Delayed cord clamping was not performed in this case. Maternal nasopharyngeal aspirate was negative for SARS-CoV-2 on the day of admission and on the fifth day. However, the mother developed symptoms of Covid-19 10 days after delivery [67]. This study suggests that SARS-CoV-2 cannot cross the placental barrier into the umbilical cord.

There are studies that have reported a positive test for SARS-CoV-2 RNA in placental tissue. It has been reported that SARS-CoV-2 can bind to angiotensin-converting enzyme 2 (ACE2) receptors in the placenta for cell entry [57; p.49-58]. The fact that SARS-CoV-2 can cross the placental barrier by binding to the ACE2 receptor supports the potential risk of mother-to-child transmission of SARS-CoV-2. Miscarriage has been reported in the second trimester in a pregnant woman who tests positive for SARS-CoV-2. The miscarriage in this study appeared to be due to placental infection with SARS-CoV-2. However, fetal samples taken from the anus, liver, thymus, and lungs tested negative for SARS-CoV-2 [51; p.100-118, 69; p.437-444]. In contrast, another study provided some evidence that SARS–CoV–2 infection of the placenta is unlikely, despite the fact that ACE2 is minimally expressed, in the placenta during pregnancy [55; p.418-423]. It has been found that some viruses, such as the Zika virus, can escape the protection provided by the placental barrier. Due to the effects of congenital Zika infection, thousands of newborns with microcephaly were reported in 2016. Six studies analyzing placental samples were negative for SARS-CoV-2 [16; pp.56-59, 31; pp.182-185, 61; pp.40-53]. These results are consistent with SARS studies, which failed to detect coronavirus in placentas [59; pp.100-107, 67]. Although SARS was not detected in

some placental samples, these placentas were reported to have increased subchorionic, intervillous fibrin, thrombotic vasculopathy, and areas of avascular chorionic villous tissue, which are associated with fetal vascular malperfusion and fetal growth restriction syndrome [55; p.100-145, 61; p. 40-53]. Despite the fact that SARS-CoV-2 RNA was detected in placental tissue in 11 studies, many researchers deny the possibility of potential transmission of SARS-CoV-2 from mother to fetus.

Conclusion of the literature review

Pregnancy is among the conditions that increase the risk of serious illness in women infected with respiratory viral infections. Pregnant patients are significantly more likely than non-pregnant patients to require intensive care, be placed on a cardiopulmonary bypass, and require mechanical ventilation, resulting in a 70% increased risk of death. The viral infection can also increase a mother's risk of developing a dangerous condition called preeclampsia and increase the likelihood of preterm birth and stillbirth. Severe respiratory viral infections further increase this risk and are associated with gestational diabetes mellitus and low birth weight. In rare cases, the virus can be transmitted to the fetus during pregnancy. Pregnancy increases the risk of severe seasonal respiratory viral infections.

As evidence of coronavirus infections such as SARS and MERS have shown severe adverse pregnancy outcomes, the effects of coronavirus-severe acute respiratory syndrome infection on pregnant women and their fetuses have attracted the attention of researchers around the world. To protect the fetus and newborn from various pathogens that may infect it during pregnancy, the placenta plays an important role as a natural barrier. There is clear evidence of Sars-CoV-2 invasion of the placenta in pregnant women in the second and third trimester, suggesting that transplacental transmission may occur. In addition, pathology criteria for the diagnosis of intrauterine transplacental infection have been published, but the number of cases is still limited, and the specific mechanism of Sars-CoV-2 invasion of the placenta in women in late pregnancy is still not completely clear, just as information about the characteristics of the uteroplacental circulation during

coronavirus infection is limited. Thus, to study the above issue, further research is needed on the structure of the placenta, the role of the placenta in the mechanism of vertical transmission of the virus in pregnant women and the protection of the intrauterine fetus. Medical personnel involved in providing medical services to women during pregnancy and childbirth need to constantly improve their knowledge and skills in the event of a new disease, regarding its characteristics in pregnant women and newborns. In most cases, the ability to take control of epidemics of future coronavirus infections and stop their further spread depends on these features.

CHAPTER II. MEMO FOR SPECIALISTS ON THE MANAGEMENT OF PREGNANT WOMEN WITH RESPIRATORY VIRAL INFECTIONS AND MODERN RESEARCH METHODS

Respiratory viral infections are the dominant group among acute human respiratory diseases with an airborne transmission mechanism, for which the localization of the pathogen and the development of the main pathological process are the respiratory tract.

Over the past three years, among respiratory viruses, the new coronavirus infection type 2, which has the most pronounced toxic course and a tendency to epidemic and pandemic spread, has the greatest practical importance.

On the International Classification of Diseases (ICD), codes for respiratory viral infections are given as follows:

According to ICD-10, the following clinical forms are distinguished:

J00 - J06 Acute respiratory infections of the upper respiratory tract

J00 - Acute nasopharyngitis (runny nose)

J02.8 - Acute pharyngitis caused by other specified pathogens

J02.9 - Acute pharyngitis, unspecified

J03.8 - Acute tonsillitis caused by other specified pathogens

J03.9 - Acute tonsillitis, unspecified

J04 - Acute laryngitis and tracheitis

J04.0 - Acute laryngitis

J04.1 - Acute tracheitis

J04.2 - Acute laryngotracheitis

J06 - Acute respiratory infections of the upper respiratory tract

multiple and unspecified localization

J06.0 - Acute laryngopharyngitis

J06 - Acute upper respiratory tract infection, unspecified

J 20.3 - acute bronchitis caused by the Coxsackie virus;

J 20.4 - acute bronchitis caused by the parainfluenza virus;

J 20.5 - acute bronchitis caused by the RS virus;

J 20.6 - acute bronchitis caused by rhinovirus;

J 20.7 - acute bronchitis caused by echovirus;

J10- J18 - Flu and pneumonia

J10 - Influenza caused by an identified influenza virus

J11 - Influenza, virus not identified.

The coronavirus outbreak has been declared a public health emergency of international concern by the World Health Organization (TRAIN) assigned the International Classification of Diseases-10 (ICD-10) codes used in emergency situations to the COVID-19 virus.

The term U07 will be changed to "emergency use codes".

U07.1 ICD-10 is awarded to a diagnosis of COVID-19 disease confirmed by laboratory tests.

U07.2 ICD-10 is assigned to the clinical or epidemiological diagnosis of COVID-19 when laboratory confirmation is inconclusive or missing.

In the International Classification of Diseases, 11th Revision, the code for a confirmed diagnosis of COVID-19 is RA01.0, and for a clinical diagnosis (suspected or probable) of COVID-19 is code RA01.2.

Memo for primary care specialists in case of ARVI and influenza manifestations in pregnant women

Influenza is a viral-bacterial disease transmitted from person to person by airborne droplets and household contact (through a handshake, through dishes, etc.). Flu symptoms: headache, malaise, sore throat, muscle pain, sore throat, fever, runny nose, nasal congestion, cough, and in some cases, vomiting and diarrhea.

At the primary health care level:

1. When caring for a pregnant woman at home, a midwife or general practitioner must assess the general condition of the pregnant woman, measure body

temperature, count respiration and pulse rates, measure A/D, assess diuresis, and find out what medications she took at home.

2. When a pregnant woman comes to the rural medical center with symptoms of ARVI and influenza, it is necessary to assess the general condition of the pregnant woman, measure body temperature, calculate respiration and pulse rate, measure A/D, assess diuresis, find out what medications she took at home.

3. If a pregnant woman has deviations of at least one of the above indicators from the norm, the pregnant woman must be urgently consulted at the central regional multidisciplinary clinic with doctors of narrow specialties (generalist, infectious disease specialist, cardiologist).

4. In case of suspected influenza, a pregnant woman must be hospitalized in a hospital for diagnosis and treatment in a hospital setting.

5. In a hospital setting, it is important for doctors to carry out a differential diagnosis with hypertension, mild preeclampsia, hepatosis of pregnancy, and cardiomyopathy.

6. In a hospital, doctors need assess the general condition of a pregnant woman, measure body temperature, count respiration and pulse rates, measure A/D, and assess diuresis. Conduct laboratory tests (blood coagulation system, blood enzyme composition, general blood test, general urinalysis, sensitivity to antibiotics). Important! Monitor pregnant women with influenza hemodynamic parameters (respiratory rate, heart rate, A/P, diuresis). In the treatment of uncomplicated influenza in pregnant women, use oral dehydration; to correct hypoxemia, use oxygen and adequate infusion therapy under the control of diuresis.

7. In the hospital, if differential diagnosis is difficult diagnosing influenza in pregnant women with hypertension, mild preeclampsia, hepatosis of pregnancy, cardiomyopathy, urgently organize a consultation with a specialist (if necessary, through the SAS).

8. In the hospital, if complications of influenza develop, organize continuous monitoring in pregnant women condition of the pregnant woman (respiratory rate, heart rate, A/P, diuresis), organize adequate infusion therapy, provide oxygen

therapy to maintain oxygen saturation up to 92-95% during pregnancy. Timely resolve the issue of the need for antibacterial therapy (with determination of sensitivity to antibiotics).

9. Beware unjustified relocation of a pregnant woman with severe influenza and additional complications from one equivalent medical institution to another. In this case, full assistance is provided with a significant delay.

Clinical characteristics of the examined pregnant women.

The study was conducted at the Specialized Maternity Center for pregnant women with Covid-19 in the Samarkand region, as well as in the laboratory of the Maternity Complex No. 1 and the private clinic “Happy Mama” in Samarkand, morphological studies were carried out at the Multidisciplinary Clinic of the Samarkand State Medical University.

We examined 155 women aged 20 to 35 years. To solve the stated problems, all patients were divided into two groups:

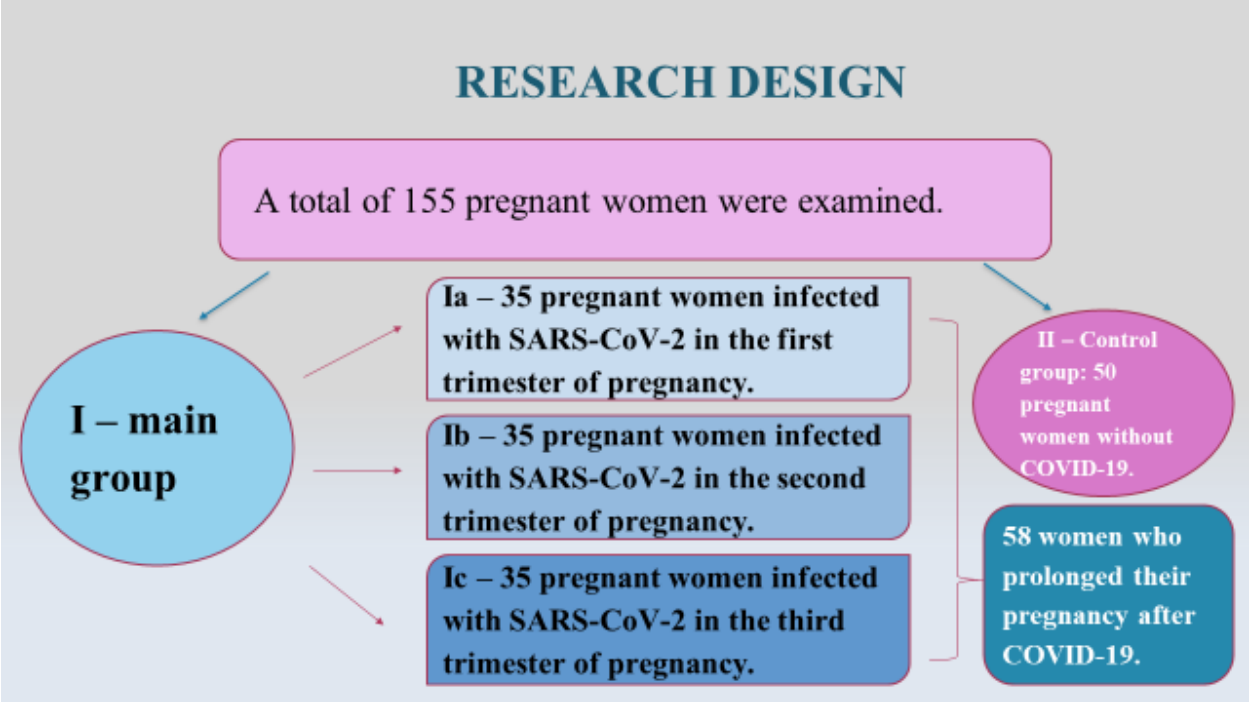
I – Main group, 105 pregnant women who had recovered from Covid-19, who were divided into 3 subgroups:

1a - 35 pregnant women who recovered from Covid-19 V I trimester of pregnancy

1b - 35 pregnant women who recovered from Covid-19 in II trimester of pregnancy

1c - 35 pregnant women who recovered from Covid-19 V III trimester of pregnancy

II – Control group made up 50 relatively healthy pregnant women**.**



Picture. 2.1. *Research material*

In addition, in 58 women of group I who had Covid-19 in different trimesters of pregnancy and remained pregnant since the first examination, it was possible to trace the further course of pregnancy and childbirth. These patients from the subgroups were distributed as follows: in subgroup 1a there were 16 women (45.7%), in subgroup 1b there were 21 patients (60%), in subgroup 1c there were 21 patients (60%).

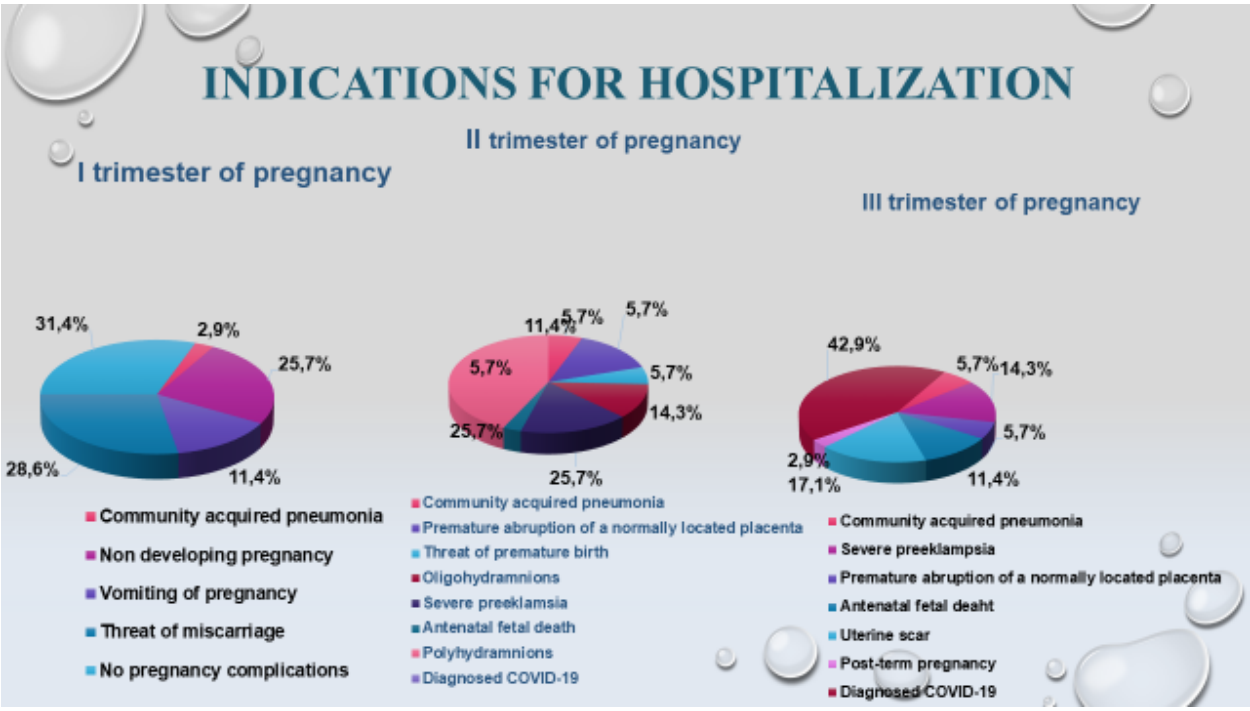
According to the severity of Covid-19 and by trimester of pregnancy, the patients were divided as follows: in the first trimester, there were 8 (22.9%) pregnant women with a mild degree of the disease; moderate severity – 20 (57.1%); severe – 7 (20%); in the second trimester, the patients were distributed accordingly: 4 (11.4%), 20 (57.1%), 11 (31.4%); in the third trimester, respectively: 7 (20%), 21 (60%), 7 (20%). Thus, more than half of pregnant patients with Covid-19 -19 (58%) had a moderate form of the disease, and every fourth pregnant woman (24%) had a severe form of Covid-19.

Indications for hospitalization (picture 2.2) in the first trimester of pregnancy were: community-acquired pneumonia (1 case - 2.9%), non-developing pregnancy

(9 cases - 25.7%), vomiting during pregnancy (4 cases - 11.4%), threatened miscarriage (10 cases - 28.6%), the remaining 11 (31.4%) patients were sent to the hospital without complications from pregnancy.

Indications for hospitalization in the second trimester were: community-acquired pneumonia, severe preeclampsia, premature abruption of a normally located placenta (2 cases each - 5.7%), antenatal fetal death (5 cases - 14.3%), threat of premature birth (9 cases - 25.7%), polyhydramnios (9 cases - 25.7%), oligohydramnios (2 cases - 5.7%), another 4 (11.4%) patients were hospitalized due to diagnosed Covid-19.

Indications for hospitalization in the third trimester were: community-acquired pneumonia (2 cases - 5.7%), severe preeclampsia (5 cases - 14.3%), premature abruption of a normally located placenta (2 cases - 5.7%), antenatal fetal death (4 cases - 11.4%), uterine scar (6 cases - 17.1%), post-term pregnancy (1 case - 2.9%). 15 pregnant women were hospitalized due to the established diagnosis of Covid-19.



Picture. 2.2. *Indications for hospitalization in the I, II and III trimester*

Modern research methods

Diagnosis of the state of the hemostasis system. The following parameters were defined: international normalized ratio (INR), D-dimer, APTT, platelet count and their aggregation function, fibrinogen, and was also carried out PCR to detect SARS-CoV-2 RNA. Laboratory diagnostics of the hemostasis system was carried out in the clinical laboratory of the Specialized Maternity Center for pregnant women with COVID-19 in the Samarkand region and in the clinical laboratory of the Maternity Complex No. 1 of the Samarkand city.

Tests to determine APTT, D-dimer, CRP and fibrinogen were performed on a portable Wondfo Fincare™ FIA Meter Plus (FS-113) pro Manufactured by Guangzhou Wondfo Biotech Co., Ltd. (Korea) using a rapid quantitative test, which is a fluorescent immunoassay, and was used in conjunction with the system Finecare™ FIA for the quantitative determination of D-dimer, fibrinogen, and aPTT in whole blood or plasma of examined patients.

Prothrombin time (PTT), prothrombin index (PTI), INR were determined using a Rayto RT-2201C (Coagulation Analyzer) device - a semi-automatic coagulometer (China). This analyzer is single-channel coagulometer for conducting studies of the hemostatic system (blood clotting) in clinical laboratories.

To obtain reliable results, blood was taken from patients in the morning, on an empty stomach, from the cubital vein, using a large-diameter needle. The first drops of blood were discarded, because... they may contain a tissue activator of the hemostatic system. To obtain platelet-poor plasma for standard coagulation studies, venous blood was collected into a plastic tube with 3.8% (0.11 mol/l) sodium citrate in a ratio of 9:1 or into vacuum blood collection systems with 3.2% (0.11 mol/l) sodium citrate, centrifuged at room temperature (18-25ºC) for 15 minutes at 3000 rpm (1200 g). The storage time of the test plasma before analysis was no more than 4 hours at room temperature and no more than 8 hours at a temperature of 2-8ºC. Since after blood collection there is a rapid change in the direction of deterioration in the condition of the sample, we tried to deliver the sample to the laboratory for testing as quickly as possible. Before analysis, 1.0 ml of distilled water was added

to the plasma vial and the contents were dissolved by gentle shaking. The plasma solution was kept at a temperature of 18-25°C for 20 minutes. To exclude the possibility of "instrumental" error, all used automatic pipettes were calibrated at the stage of laboratory analysis.

The frequency of tests depended on the severity of the patients' condition. If the condition of the patients corresponded to a mild degree of severity of the disease, then tests were taken on average every 4-5 days. If the condition corresponds to moderate severity - every 1-2 days. In severe cases of the disease, these tests were performed daily, and extraordinary tests were also performed when the patient's condition worsened.

Method for determining endothelin-1 (ET-1). Endothelin-1 is currently considered the most important mechanism regulating the function of the vascular endothelium. Due to the fact that endothelin-1 and vascular endothelial cells are regulators of vascular tone, which plays an important role in the pathogenesis of circulatory disorders in the fetoplacental system.

In all examined pregnant women, endothelin-1 was determined in the blood serum at the private medical clinic "Happy Mama" using the enzyme immunoassay method. Blood collection from the examined patients was carried out in the morning, on an empty stomach, at rest from a vein into a test tube containing a solution of sodium citrate. After this, the tube with blood was placed in a special refrigerator and transported to the clinical laboratory. The tube with blood was centrifuged for 10 minutes at a speed of 1000 rpm. Samples for examination were stored at a temperature of - 36^0From before analysis. The concentration of ET-1 is determined using an enzyme-linked immunosorbent assay; for this study, tests from the Biomedical ENDOTELIN (1-21) system of BioKhimMak CJSC were used.

Ultrasonographic methods. Ultrasonographic studies: ultrasound examination of the uterus and fetus, as well as Doppler examination of the utero-placental complex in all examined pregnant women were carried out in the Specialized Maternity Center for pregnant women with Covid-19 and repeated studies were carried out in the X-ray radiology department of the multidisciplinary

clinic of Samarkand State Medical University on the Mindray DC-70 X-nsight ultrasound machine (Shenzen Mindray BIO-MEDICAL Electronics CO. LTD. Korea) using transabdominal and transvaginal convex sensors, with a frequency of 3.5-7.5 MHz in four-dimensional gray scale scanning mode.

Ultrasound placentography was carried out by determining the location of the placenta, its thickness and structure. To characterize the structure of the placenta, the classification of Granum et al was used. (1979) [22], according to which there is a IV degree of placental maturity.

Ultrasound was performed with the woman lying on her back. The first step was to determine the position of the fetus and the presenting part. After this, fetometry was performed: BPS of the head, abdominal circumference was determined with clear visualization of the umbilical vein, and the length of the femur.

Using a Doppler study, the functional state of the vessels of the feto-placental system and the state of blood flow in the large vessels of the uterus and fetus were assessed, starting from the 16-17th week of pregnancy, using a special Doppler sensor of the same Mindray DC-70 X-nsight ultrasound device in a special color Doppler scanning mode.

Dopplerography assessed blood flow in the right and left uterine arteries, spiral arteries, as well as in the umbilical cord arteries and its terminal branches, the middle cerebral artery and the fetal aorta, and, if necessary, in the ductus venosus. Circulatory disorders were diagnosed in these vascular beds and this had a high prognostic value in diagnosing the development of placental insufficiency, intrauterine hypoxia and fetal growth restriction syndrome.

To assess the blood circulation velocity curves in the studied vessels, the generally accepted independent indicators were calculated: systolic-diastolic ratio - SDR (systolic-diastolic ratio), resistance index - ReI (resistance index) and ripple index - RiI (pulsation index). Calculations were carried out using the formulas:

SDR = msbfv/edbfv; ReI = (MSBFV-EDBFV)/MSBFV; RiI = (MSBFV-EDBFV)/ABFV;

MSBFV – maximum systolic blood flow velocity

EDBFV – end diastolic blood flow velocity

ABFV – average blood flow velocity.

Blood flow disorders in the feto-patient complex were assessed based on the classification proposed by A.N. Strizhakov et al. (1986) [35]:

- No disturbances in uteroplacental-fetal blood flow were detected.
- A single twist of the umbilical cord around the fetal neck.

1st degree – compensated disturbance of placental circulation, normal state of fetal hemodynamics.

1A – violation of uteroplacental blood flow with normal fetal-placental blood flow;

2B – violation of fetal-placental blood flow with normal uteroplacental blood flow;

2AB – combined disorder of uteroplacental and fetal-placental blood flow;

2-degree – compensated or sub compensated disturbance of fetal hemodynamics without disturbance of fetal-placental blood flow or in combination with disturbance of fetal-placental blood flow that does not reach critical values.

3-degree – decompensated disturbance of fetal hemodynamics without a critical disturbance of fetal-placental blood flow or in combination with a critical disturbance of fetal-placental blood flow.

Morphological research methods. All women who gave birth underwent macroscopic and microscopic examination of the placentas (if pregnancy was terminated in the first trimester, a histological examination of the contents of the uterine cavity was performed). Histological examination was carried out on paraffin serial sections in the department of pathological anatomy of the Multidisciplinary Clinic of Samarkand State Medical University (head of department, PhD, associate professor Zhumanov Z. E.).

Morphological and histological studies were carried out on materials from the contents taken from the uterine cavity during curettage of the uterine cavity in connection with an undeveloped pregnancy and after incomplete spontaneous

abortions, as well as after artificial termination of pregnancy in the early stages. For histological examination, the examined material was fixed in 10% formalin and, according to the generally accepted method, was carried out in a tissue processor; paraffin and sections 4–5 μm thick were embedded in a special apparatus. stained with hematoxylin and eosin. In stained histological preparations, the degree of damage to the vessels of the chorionic villi, changes in its tissue structures, and the nature of their damage were assessed.

After premature or term birth, placental tissue was collected for histological analysis after careful macroscopic examination. For histological examination, material was taken from the central and marginal areas of the placenta (1 cm in size^3). Using the classical method according to O.V. Volkova and Yu.K. Eletsky [9], fixation was carried out in 10% neutral formalin, then the organ was washed, dehydration was carried out in an alcohol battery, and paraffin was poured in with a special apparatus. After this, 6-μm-thick sections of the placenta were obtained and then stained with hematoxylin and eosin using a LEICA RM 2245 rotary microtome. The sections were studied under a LEICA light microscope with a digital camera (magnification: 20 x approx. 10, 40 x approx. 10), the structure of the villi and intervillous space, the diameter of the vessels and the state of the vascular wall, the state of the terminal villi and syncytiocapillary membranes were described. Morphological parameters were assessed in 50 sections of each placenta.

Statistical processing of research materials. Statistical processing and storage of research materials were carried out in the Microsoft Excel 2007 database using the Statistica 10 program. Data were expressed as: mean (M) ± standard deviation (m). To determine the statistical significance of differences in continuous values depending on the type of distribution, the Student (t) test (for parametric distribution) and the Kolmogorov–Smirnov test, Mann-Whitney U test (for nonparametric distribution) were used.

When comparing discrete variables, the $\chi 2$ test and Fisher's exact test were used. To assess the correlation between quantitative characteristics, linear regression methods and correlation analysis (Pearson, Spearman correlation coefficient) were

used. Differences and correlations were considered statistically significant at $p<0.05$.

The reliability (p) of the compared values is determined by the table of factorials using the χ criterion^2, calculated using the Holdene formula: $\chi^2= Wy^2c$ taking into account one degree of freedom – df=1, where after transformation the final formula takes the following form:

$$\chi^2= \frac{\left[\frac{((a+0.5)x(d+0.5)^2}{(b+0.5)x(c+0.5)}\right]}{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}$$

If at least one of the values a, b, c, d is equal to 1, then the reliability of differences in the frequency of occurrence of genes and haplotypes is calculated using χ^2 Yates' correction for sample continuity:

$$\chi^2= \frac{(axb+bxc)^2\ xN}{(a+b)x(c+d)x(a+c)x(b+d)}$$

χ value^2, exceeding 3.841 (which corresponds to $p<0.05$) is considered as an indicator of a significant difference between the frequency characteristics in the compared groups.

CHAPTER III. RISK FACTORS, CLINICAL MANIFESTATIONS AND TREATMENT METHODS FOR PREGNANT WOMEN WITH RESPIRATORY VIRAL INFECTIONS

3.1. Clinical characteristics of the examined women and risk factors for infection

As stated above, the main group consisted of 105 pregnant patients who had COVID-19 at different stages of pregnancy and were prospectively monitored. The age of the patients was 20-35 years, i.e. The pregnant women were of active reproductive age, the average age was 27.1±3.1 years.

The control group consisted of 50 pregnant women without COVID-19. All 50 patients included in the study were also of active reproductive age, from 20 to 35 years. The average age was 25.2±2.1, which does not differ significantly from the main group of subjects.

By place of residence, 57 (54.3%) of the examined women in the main group were residents of the city, and in the control group, 29 (58%) women were residents of the city, which also did not have significant differences from the examined women of the main group.

The social structure of the surveyed women is presented in Table 3.1.

Table 3.1

Social structure of surveyed women, (abs., %)

Indicator	Main group n=105 abs. (%)	Control group, n=50 abs. (%)
Housewives	48 (45,7%)	17 (34%)
Workers	21 (20%)	12 (24%)
Female agricultural workers	28 (26,7%)	16 (32%)
Female students	8 (7,6%)	5 (10%)

Table data 3.1 show that 45.7% (almost half!) of those sick with COVID-19 were housewives, in contrast to the control group (34%). This indicates a failure to

comply with standard precautions for the prevention of viral infection during a pandemic - women who were not working, were at home, and were not in contact with a large number of people became infected, despite the active promotion of the principles of social protection among the population.

From the gynecological history it was found that the average age of menarche in women of the main group was 12.1±0.6 years, with fluctuations from 11 to 14 years, which does not distinguish these patients from the general population of women. The average age at the onset of sexual activity was 20.6±2.1 years.

The average age of menarche in patients in the control group also did not differ significantly from the age of patients in the main group and was 12.3±0.5 years (p=0.001). We obtained similar data regarding the average age of onset of sexual activity: 18.3 ± 1.1 years (p = 0.05).

There were 38 (36.2%) primigravid women in the main group, 20 (40%) in the control group, and 67 (63.8%) and 30 (60%) multipregnant women, respectively. Comparative data on the reproductive function of women in the main and control groups are presented in Table 3.2.

As can be seen from the table above, multipregnant and multiparous women with Covid-19 had a history of complications in previous pregnancies in almost half of the observations (49.3%). Of particular note are another 49.3% of women who had a history of repeated spontaneous and induced abortions. It should be noted that women in the control group had a significantly lower frequency of induced and spontaneous abortions, and complications such as trophoblastic disease and placenta previa were not noted at all in the anamnesis of patients in the control group. The proportion of women with a uterine scar after a cesarean section who had a history of obstetric hemorrhage, ectopic pregnancy and preeclampsia differed significantly from the data of patients in the main group (χ^2=0,10, P=0,753; χ^2=0,00, P=0,968).

Table 3.2.

Parity and outcomes of previous pregnancies of the examined women, (abs, %)

Indicator	Main group (n=67) abs. (%)	Control group (n=30) abs. (%)	χ^2	P	OR	DI min	DI max
Urgent birth:	49 (73,1%)	24 (80%)	0,02	0,876	0,95	0,48	1,86
1	19 (28,4%)	8 (26,7%)	0,00	0,976	1,01	0,41	2,54
2-3	23 (34,3%)	11 (36,6%)	0,02	0,882	0,94	0,41	2,13
4 or more	7 (10,4%)	5 (16,7%)	0,01	0,925	0,95	0,31	2,93
Premature birth	17 (15,4%)	6 (20%)	0,68	0,408	1,52	0,56	4,09
Spontaneous abortions (including non-developing pregnancy):1	17 (25,4%) 14 (20,9%)	3 (10%) 2 (6,7%)	3,19	0,074	3,69	0,81	16,92
2 or more	3 (4,5%)	1 (3,3%)	0,10	0,753	1,44	0,15	14,21
Artificial termination of pregnancy:1	16 (23,9%) 9 (13,4%)	3 (10%) 2 (6,7%)	1,07	0,300	2,25	0,47	10,82
2 or more	7 (10,4%)	1 (3,3%)	1,51	0,220	3,50	0,42	29,25
Ectopic pregnancy	3 (4,4%)	1 (3,3%)	0,10	0,753	1,44	0,15	14,21
Bubble drift	1 (1,5%)	-	0,48	0,489	-	-	-
C-section	7 (10,4%)	4 (13,3%)	0,09	0,762	0,82	0,23	2,95
Preeclampsia/eclampsia	2 (3%)	1 (3,3%)	0,00	0,968	0,95	0,08	10,75
PANLP	3 (4,4%)	1 (3,3%)	0,10	0,753	1,44	0,15	14,21
Placenta previa	1 (1,5%)	-	0,48	0,489	-	-	-
Postpartum hemorrhage	5 (7,5%)	1 (3,3%)	0,69	0,405	2,45	0,28	21,55

***Note**: χ^2, P - significance of differences in indicators of the main group compared to the control group*

Taking into account the burden of obstetric history, we analyzed previously used contraceptive methods (Table 3.3).

Table 3.3

Previously used contraceptive methods of surveyed women (abs., %)

Method of contraception	Main group, (n=67)		Control group, (n=30)	
	abs.	%	abs.	%
Intrauterine device	7	10,4	13	43,3
Condom	10	15	4	13,3
Coitus interruptus	13	19,4	2	6,7
Hormonal methods	3	4,5	5	16,7
Not used	34	50,7	6	20

The analysis of women from the main and control groups once again demonstrates, unfortunately, the low commitment of women in Samarkand and the Samarkand region to the prevention of unwanted pregnancy - more than half of those surveyed did not use contraceptive methods, and every third woman used ineffective methods of protection against unwanted pregnancy.

Data on concomitant somatic pathology (Table 3.4) demonstrate existing information that the more severe the premorbid background, the higher the risk of infection and severe course of COVID-19. According to our data, all those infected with SARS-COV-2 had chronic hypochromic anemia of varying severity, every third patient was obese and every 10th had chronic venous insufficiency, as well as inflammatory diseases of the urinary system. It should be especially noted that 14 women, accounting for 13.3%, had a combination of two or more somatic diseases. The table data indicates a significantly lower frequency of somatic pathology in women who did not get sick with COVID-19 compared to those who got sick. Thus, we can also consider the burden of the somatic status of pregnant women as one of the risk factors for contracting a viral infection.

Table 3.4

Somatic diseases in examined pregnant women, (abs., %)

Disease	Main group (n=105) Abs., (%)	Control group (n=50) abs., (%)	χ^2	P	OR	DI min	DI max
Anemia	105 (100%)	15	94,94	0,000	-	-	-

		(30%)					
Obesity	34 (32,4%)	2 (4%)	15,30	0,000	11,49	2,64	50,11
Urinary tract infections	11 (10,5%)	1 (2%)	3,41	0,065	5,73	0,72	45,72
Varicose veins	10 (9,5%)	1 (2%)	2,91	0,088	5,16	0,64	41,47
Chronic respiratory infections	5 (4,8%)	1 (2%)	0,10	0,753	1,44	0,15	14,21
Diseases of the hepatobiliary system	3(2,4%)	1 (2%)	0,10	0,753	1,44	0,15	14,21

Note: *χ^2, P - reliability of differences in indicators of the main group in comparison with the control group*

The study of gynecological history revealed a significant difference in the frequency of gynecological diseases in women of the main and control groups (Table 3.5).

From the information specified in table. Table 3.5 shows that the most common gynecological diseases in the main group of patients were infections of the vulva and vagina and inflammatory diseases of the uterus and appendages, which amounted to a total of 71.5%. It should be noted that 81% of the examined women of the main group had more than one gynecological disease in their history and at the present time, and only 19% of young women of reproductive age had no history of gynecological diseases at all. Analysis of this table indicates a more favorable gynecological background in those pregnant women who were not infected with SARS-CoV-2.

Thus, the somatic, obstetric and gynecological anamnesis of women in the control group indicate a statistically lower susceptibility to infection with SARS-CoV-2.

Table 3.5

History of gynecological diseases in the examined women, (abs., %)

Disease	Main group (n=105) abs., (%)	Control group (n=50) abs., (%)	χ^2	P	OR	DI min	DI max

Infections of the vulva and vagina	53 (50,5%)	7 (14%)	18,995	0,000	6,26	2,58	15,18
Inflammatory diseases of the genitals	22 (21%)	5 (10%)	2,824	0,093	2,39	0,85	6,73
Cervical diseases	22 (21%)	3 (6%)	5,598	0,018	4,15	1,18	14,61
Infertility	11 (1,05%)	2 (4%)	1,849	0,174	2,81	0,60	13,18
Uterine fibroids	4 (3,8%)	1 (2%)	0,355	0,551	1,94	0,21	17,83
Ovarian cysts and cystomas	1 (0,95%)	1 (2%)	0,292	0,589	0,47	0,03	7,69
Absence of gynecological diseases	20 (19%)	36 (72%)	41,157	0,000	0,09	0,04	0,20

***Note**: χ^2, P-significance of differences in indicators of the main group compared with the control group*

Among the complications of the gestational process in pregnant women with coronavirus infection in early pregnancy, vomiting of pregnancy should be noted, which occurred in 31 patients (29.5%). The threat of interruption was noted in 10 (9.5%) women.

Upon admission to the hospital, the condition of 25 (23.8%) women was assessed as serious. 28 (26.7%) patients had complications during labor in the form of untimely rupture of amniotic fluid, inconclusive condition of the fetus, and prolonged labor, which, against the background of acute coronavirus infection, required expanding the indications for abdominal delivery.

According to our data, pregnancy outcomes during the development of coronavirus infection were as follows: spontaneous termination of pregnancy before 22 weeks, as well as non-developing pregnancy occurred in 14 (13.3%) cases. Artificial termination of pregnancy was performed in 5 (4.8%) cases. Due to antenatal fetal death, induction of labor in the second and third trimester was performed in 9 (8.6%) cases. Preterm birth due to obstetric complications (severe preeclampsia, PANLP), as well as due to the severity of the mother's condition

(community-acquired pneumonia) occurred in 24 (22.9%) women. Thus, pregnancy ended in term birth only in 62 (59%) patients with COVID-19. 39 (45.3%) women delivered spontaneously through the natural birth canal. Caesarean section was 54.7% and occurred in 47 patients.

As stated above, the main group consisted of 105 pregnant women with COVID-19 who were in the Specialized Maternity Center for Pregnant Women with COVID-19 in the Samarkand Region, where Kim V.S. was the temporary chief physician. (chief doctor of maternity complex No. 1 of the city of Samarkand). Of these, 25 (23.8%) pregnant women had a severe form of the disease, 61 (58.1%) had a moderate form of the disease and 19 (18.1%) had a mild form of COVID-19; all women were discharged in satisfactory condition after recovery. During the period August-September 2021 (collection of material in the hospital), maternal mortality due to COVID-19 was not registered in this medical institution.

A total of 86 newborns were born. Of these, 61 (70.9%) were full-term, 24 (27.9%) were premature. One newborn (1.2%) had signs of postmaturity and was born at 43 weeks' gestation. 9 (8.6%) died antenatally, another 6 (5.7%) died postnatally (extreme prematurity, PANLP). Perinatal mortality was 143‰.

Pregnancy outcomes in the control group of patients: term birth – 46 (92%), premature birth – 4 (8%). Vaginal delivery occurred in 45 (90%) women, cesarean section was performed in 5 (10%), 4 of these patients had a scar on the uterus after a previous cesarean section, in 1 case a cesarean section was performed due to the inconclusive condition of the fetus. The main indication for abdominal delivery was a complicated obstetric history and a scar on the uterus.

In this group, 50 live newborns were born with an average Apgar score in the first minute of 7.1 ± 1.0 points. No perinatal mortality was recorded.

Thus, the risk factors for SarS-CoV-2 infection in our study were: unfavorable somatic background, parity, as well as complicated obstetric and gynecological background.

3.2. Clinical manifestations of respiratory viral infections in examined pregnant women and treatment methods

The main symptoms of Covid-19 in the examined group of pregnant women were: increased temperature and fever in 101 (96.2%) women; weakness in 87 (82.9%); dry cough in 56 (53.3%); disturbance of smell and taste in 52 (49.5%); myalgia in 23 (21.9%) women; headache in 21 (20%) women; sore throat in 17 (16.2%), runny nose (rhinorrhea) also in 17 (16.2%) women; diarrhea in 9 (8.6%); palpitations in 54 (51.4%) women.

Thus, the most common symptoms of Covid-19 in the pregnant women we examined were fever, weakness, dry cough, impaired sense of smell and taste, which manifested themselves more than in every second patient. The main clinical manifestations of severe COVID-19 in 25 pregnant women were: fever and temperature above 38°C in 100% of women; weakness in 96%; shortness of breath in 88%; multiple organ failure 0.95% (1 patient). All patients with a severe form of the disease underwent a CT scan of the chest before hospitalization and more than 50% of lung tissue damage was detected.

Basic laboratory data performed on pregnant women in connection with diagnosed Covid-19 are presented in table. 3.6.

Table 3.6

Main laboratory parameters in the examined women, (M±m)

Indicator	Main group (n=105)	Control group (n=50)	P
C-reactive protein (mg/l)	41,1±2,8	8,5±2,2	<0,001
Platelets (10^9 /l)	144,8±21,2	180,1±18,5	>0,5
Leukocytes (10^9 /l)	12,8±1,2	10,7±2,2	>0,5

Note: *P-significance of differences in the indicators of the main group in comparison with the control group.*

The diagnosis of Covid-19 was established on the basis of a detailed assessment of clinical data, epidemiological history, general examination with assessment of the condition of the skin and mucous membranes, auscultation and

percussion of the lungs, palpation of lymph nodes, palpation of the abdominal organs and, if possible, determination of the size of the liver and spleen, thermometry, measurement of heart rate, respiration, blood pressure measurement, pulse oximetry. In addition to the laboratory tests generally accepted in obstetrics (general blood and urine analysis, blood group and Rh factor, blood biochemistry, coagulogram), we performed a PCR test for all pregnant women to detect SARS-CoV-2 RNA, and an ECG. According to indications (suspicion of community-acquired pneumonia), a CT scan of the chest (lungs) was performed before hospitalization.

Based on the spectrum of clinical symptoms and laboratory data, we determined the severity of the underlying disease and, based on this, treated the underlying disease.

Treatment methods for Covid-19 in hospitalized pregnant women

Treatment of hospitalized pregnant women with Covid-19 was carried out according to the "Temporary recommendations for the management of patients infected with coronavirus infection Covid-19" of the Ministry of Health of the Republic of Uzbekistan (version 8, 2021) [11].

Pregnant women with Covid-19				
Clinic	Mild course	Medium-heavy	Severe course	Extremely severe course
Pregnant women in the first trimester	It is carried out in the same way as outside pregnancy. Outpatient observation. Treatment is symptomatic.	Considering the embryotoxicity of the virus and iatrogenic effects, it is possible to offer medical termination of pregnancy after treatment.	Considering the embryotoxicity of the virus and iatrogenic effects, it is possible to offer termination of pregnancy through medical abortion after cure.	Considering the embryotoxicity of the virus and iatrogenic effects, it is possible to propose termination of pregnancy after treatment.

Pregnant women in the second trimester	It is carried out in the same way as outside pregnancy. Outpatient observation. Treatment is symptomatic. It is preferable to lie on your left side.	It is carried out in the same way as outside pregnancy. Termination of pregnancy is not indicated. Antiviral, antibacterial, detoxification therapy, respiratory support - according to indications. Lie on your left side.	It is carried out in the same way as outside pregnancy. It is preferable to lie on your left side.	It is carried out in the same way as outside pregnancy. Up to 20 weeks, an emergency caesarean section may not be performed, because the gravid uterus does not affect cardiac output. For non-intubated patients, it is preferable to lie on the left side.
Pregnant in the third trimester	The 3rd stage of labor should be carried out actively, and bleeding should be prevented in the postpartum period. Caesarean section is performed according to obstetric indications. In the postpartum period, observe measures to prevent transmission of the virus from mother to child by observing	The 3rd stage of labor should be carried out actively, and bleeding should be prevented in the postpartum period. Caesarean section is performed according to obstetric indications. In the postpartum period, observe measures to prevent transmission of the virus from mother to child by observing protective	Childbirth is carried out under maximum anesthesia and exclusion of the second stage of labor. In order to speed up labor and prevent the development of respiratory and cardiovascular failure, it is possible to use exit obstetric forceps or a vacuum extractor. Prevention of bleeding in the postpartum	For non-intubated patients, it is preferable to lie on the left side. Emergency caesarean section is indicated if it is impossible to eliminate hypoxia due to mechanical ventilation or with progression of respiratory failure, development of alveolar pulmonary edema and refractory septic

	protective measures. Breastfeeding is possible	measures. It is preferable to feed the newborn with expressed milk.	period. Follow measures to prevent transmission of the virus from mother to child. Feeding a newborn with expressed milk	shock. In the postpartum period, observe measures to prevent transmission of the virus from mother to child by observing protective measures. It is preferable to feed the newborn with expressed milk.
Not recommended: - delayed cord clamping; - mother-child skin-to-skin contact is not recommended; - the baby is not put to the breast to prevent postnatal infection. Recommended: - all patients, regardless of the stage of pregnancy, are recommended to prevent bleeding; - remove the child from the delivery room as quickly as possible; - termination of pregnancy due to severe complications of COVID-19 before and after 24 weeks of pregnancy is carried out only for obstetric indications. A positive COVID-19 status in itself is not an indication for a cesarean section. Early delivery in the agonal state of the pregnant woman and the living fetus is recommended to be carried out at 28-32 weeks of pregnancy. The scope of surgical intervention is decided by a council strictly in accordance with specific medical indications.				
Symptomatic therapy: • Zinc preparations 100 mg once a day for 10 days; • Vitamin D preparation 5000 units once a day; • Vitamin C 500 mg per day; • Fluid consumption 40 ml per 1 kg of weight; fractional enriched protein meals 4-5 times; light physical activity and breathing exercises. • Reducing temperature: Paracetamol tablet 500 mg at temperatures above 38.5ºC no more than 3 times a day • Antitussive drugs (according to indications) (rengalin 2 tablets 3 times a day under the tongue; libexin 1 tablet 3 times) • or gargling and nasal rinsing • Acetylsalicylic acid or clopidogrel 75-150 mg 1 time a day (according to indications); • Drink plenty of fluids. • Rational, easily digestible nutrition – 5 times a day • Light physical activity (breathing exercises				

CONCLUSION ON CHAPTER III

Thus, by the time of contracting a viral infection, pregnant women had an unfavorable somatic, as well as obstetric and gynecological background, which could not but affect the course of pregnancy with the development of a somatic disease. The somatic, obstetric and gynecological anamnesis of women in the control group indicate a statistically lower susceptibility to infection with SARS-CoV-2.

Clinical manifestations of viral infection in pregnant women examined by us were basically no different from non-pregnant women and from general papulation in general, and the severity of the disease depended on the existence of somatic risk factors such as iron deficiency anemia, obesity, varicose veins, gynecological diseases such as infections of the vulva and vagina, inflammatory diseases of the genitals and cervical diseases, as well as complications of previous pregnancies.

The treatment of hospitalized and examined pregnant women with Covid-19 was carried out on the basis of the “Temporary recommendations for the management of patients infected with coronavirus infection Covid-19” approved by the Ministry of Health of the Republic of Uzbekistan, Version 8, 2021.

CHAPTER IV. MOTHER-PLACENTA-FETUS SYSTEM IN PREGNANT WOMEN WITH RESPIRATORY VIRAL INFECTIONS

4.1. The state of blood circulation in the mother-placenta-fetus system in women with respiratory viral infections

Due to the fact that viral infection in the mother is one of the risk factors for the development of adverse outcomes for the fetus, we conducted ultrasound/Doppler studies of pregnant women who had Covid-19 in different trimesters of pregnancy. Ultrasound/Doppler studies were performed at 16-24, 28-34, 38-40 weeks of pregnancy upon admission and after discharge. The state of fetal-placental blood flow was determined using the systole-diastolic ratio (SDR). Impaired blood flow in the umbilical cord artery was determined by the presence of an increase in SDR values above the 95% percentile of its norm. Impaired blood flow in the fetal middle cerebral artery was diagnosed when a decrease in numerical SDR values was detected to be less than 5% percentile of normal. Assessment of the functional state of the fetoplacental complex was carried out using ultrasound and Doppler examination.

The mother-placenta-fetus system in women who have had Covid-19 in the first trimester of pregnancy.

In total, we observed 35 patients in the first trimester, of which there were 8 (22.9%) with mild disease; moderate severity – 20 (57.1%); severe – 7 (20%). Pregnancy was terminated in the first trimester in 19 (54.3%) (spontaneous termination of pregnancy, as well as pregnancy loss in 14 (40%) women, artificial termination of pregnancy was performed in 5 (14.3%) cases). 16 women prolonged their pregnancy; we also observed them in the second and third trimesters. Of these 16 patients, 8 (50%) suffered a mild form of the disease; moderate severity – 6 (37.5%); severe – 2 (12.5%).

Information about fetometry in the first trimester is presented in table. 4.1.

Table 4.1

Indicators of fetometry of fetuses of patients with Covid-19 at 11-12 weeks of pregnancy, (M±m)

Indicator/groups	Main	Test	P
BPS	16,4±1,0	19,1±0,9	<0,75
CTS	7,5±0,6	8,3±0,6	>0,5
LF	8,3±0,6	10,5±0,7	<0,62

Note: *P – significance of differences between the main and control groups*

As the information shows, no significant difference in the growth and development of fetuses in the first trimester of pregnancy was found in the examined women with COVID-19 compared to patients in the control group. However, ultrasound examinations later in the first trimester revealed significant deviations from the normal structure of the placenta in pregnant women with COVID-19, which ultimately led to spontaneous abortion and non-development pregnancy in 14 (40%) women.

With ultrasound of these women up to 16 weeks, we had information about the pathological course of the first trimester of pregnancy in 40% of cases, which manifested itself in a decrease in the amnion cavity in all 14 patients, which had significant differences with the control group ($p<0.05$), as well as with the group of women who underwent artificial termination of pregnancy at will ($p<0.05$). In addition, in 5 (14.3%) women observed in the first trimester of pregnancy, hypoechoic zones and thinning of the chorion were found, which was regarded as inflammation (chorionitis) - Pic. 4.1.

Picture 4.1. *Ultrasound examination of patient S., patient case No. 116. Diagnosis: Pregnancy 11-12 weeks. Acute Covid-19, moderate severity - on Ultrasound – hypoechoic zones and thinning of the chorion*

Thus, when monitoring the course of pregnancy in women with COVID-19 in the first trimester of pregnancy, ultrasound data revealed signs of impaired placental formation in 40% of those examined, which later manifested itself as both non-development pregnancy and spontaneous abortion. It should be especially noted that these outcomes occurred in moderate (10 women) and severe (4 women) coronavirus infection, which allows us to draw a conclusion about the influence of acute severe and moderately severe coronavirus infection on the formation of the placenta. The results of this section of the study allowed us to conclude that the course of pregnancy was more favorable *with mild form covid-19,* as well as about the compensatory capabilities of the utero-fetal circulation in early pregnancy.

Currently, information on the incidence of non-development pregnancy in COVID-19 is still fragmented. A number of studies do not confirm their direct connection with coronavirus infection [25]. An interesting observation is that the presence of symptoms during the acute phase of COVID-19 appears to correlate with an increased risk of non-development pregnancy in those infected with SARS-CoV-2 [2]. This is consistent with the modern concept of risk factors for non-development pregnancy, which include fever above 38°C [38].

Analyzing the information available in the available literature, it can be assumed that SARS-CoV-2 is more likely not a direct etiological factor, but a pathogenetic confounder that affects the outcome of early pregnancy in a particular individual. To summarize, we can conclude that almost 4 years of the existence of Covid-19, the relevance of an in-depth study of the consequences of coronavirus infection, including its impact on the health of pregnant women and the reproductive health of women of fertile age in general, is growing. In connection with the above, we have compiled a Program for identifying risk factors for non-development

pregnancy in women with Covid-19 (DGU No. 15692, Approved by the Intellectual Property Agency of the Ministry of Justice of the Republic of Uzbekistan, 03/26/22).

Based on the implementation of a program to determine risk factors for non-development pregnancy in women infected with SARS-CoV-2, the practical need for a detailed examination of patients before prescribing drugs and further dynamic monitoring with the mandatory determination of certain laboratory blood parameters has been substantiated.

This program is intended for an objective assessment of the selected safest method of treating pregnant women during a pandemic, provides for the need for a dynamic examination of the pregnant woman's condition, and also to use it in the development of seasonal viral infections (see Application 1).

Based on the data obtained, a score was determined for the degree of risk of developing non-development pregnancy, and on this basis, tactics for managing pregnant women in the first trimester in the context of the Covid-19 pandemic/epidemic of seasonal viral infections were developed.

0-6 points – low risk of non-development pregnancy. No special treatment is required. Standard treatment of the underlying disease is required.

7-15 points – average risk of non-development pregnancy. L-arginine preparations and pregnancy-preserving therapy are added to the standard treatment of the underlying disease.

16 and more – high risk of non-development pregnancy. Low molecular weight heparin drugs are added to the standard treatment of the underlying disease in a prophylactic dose (Clexane 0.4-0.6 subcutaneously) for 4-6 weeks (the dose of the drug depends on the severity of the disease and the patient's weight). As well as pregnancy-preserving therapy and L-arginine preparations.

As a result of the study, it was found that 14 women (13.3%) from the group with UP scored a total of 16 points or more, while 91 women (86.7%) scored a total of 6 points or less. The sensitivity of the program we developed was 86.7%. It was also revealed that 45 (90.0%) women from the control group without non-

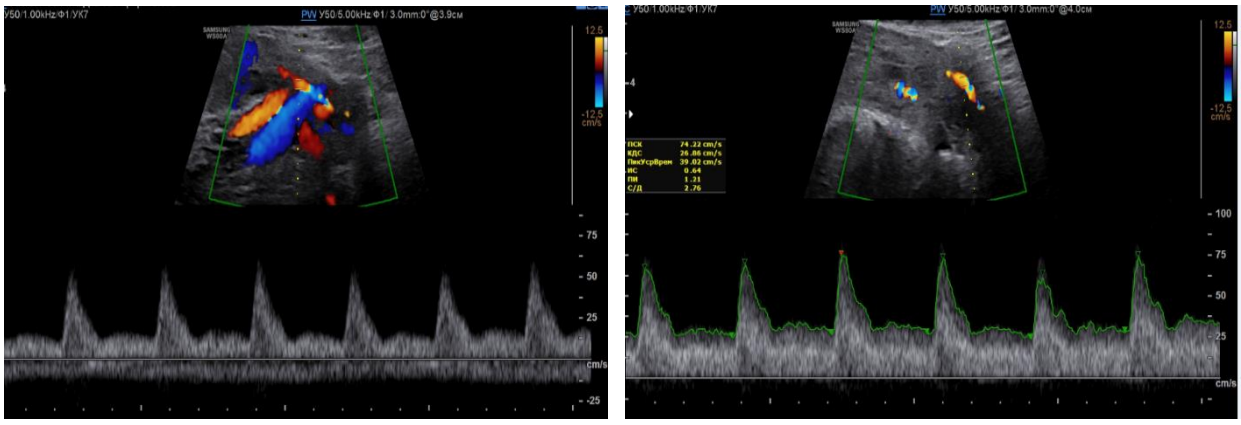
development pregnancy scored a total of 6 points or less, while 5 women (10.0%) scored a total of 7 and 15 points. The specificity of the program we developed was 90.0%.

Uteroplacental and fetal placental circulation in-women with Covid-19 in the second trimester of pregnancy.

In this group, an analysis of the clinical and anamnestic data of all 35 pregnant women was also carried out, the features of the course of this pregnancy were studied, fetometry and placentography were performed during an ultrasound examination, the functional state of the uteroplacental system was assessed using Doppler examination, and the course and outcomes of childbirth and their dependence on morpho-functional changes in the placenta were analyzed.

During ultrasound examination premature maturation of the placenta detected in 20% (7) of pregnant women, and in women who had a severe form of coronavirus infection. Oligohydramnion detected in 2 (5.7%), polyhydramnios was diagnosed in 9 (25.7%). In most cases of Covid-19 disease in the second trimester of pregnancy, a normal echographic structure of the placenta is detected - 28 (80%) and the amount of amniotic fluid - 24 (68.6%).

In a Doppler study, the indicators of uteroplacental and fetal placental circulation in 19 (54.3%) women in this subgroup were similar to studies of pregnant women without coronavirus infection (Picture 4.2), i.e. no hemodynamic disturbances were found in them.



Picture 4.2. *Doppler analysis of the uteroplacental circulation of patient K., 25 years old. Pregnancy 28 weeks. Covid-19, moderate to severe. PI in UA is 2.05 on the right and 1.21 on the left (normal PI at 28 weeks is 1.06).*

During a Doppler study in this group of pregnant women, it was found that in 16 (45.7%) cases there was an increase in vascular resistance in the uterine, spiral arteries and in the umbilical cord artery. Of these, 11 (31.4%) women had a clinically severe form of Covid-19, and 5 (14.3%) had a moderate form. In table Table 3.3 presents data on the frequency of circulatory disorders in the mother-placenta-fetus system in these women.

Table 4.2

Frequency of detected disorders in the mother-placenta-fetus system in patients of group Ib (n=16), (abs.,%)

Types of violations	abs., (%)
Intraplacental circulation disorders	2 (5,7%)
Circulatory disorders in the uterine and spiral arteries	11 (31,4%)
Circulatory disorders in the umbilical artery	3 (8,6%)

The data in Table 4.2 shows that only two patients with Covid-19 in the second trimester had a violation of the intraplacental circulation and three had a violation of the fetal-placental circulation, while disturbances in the uteroplacental circulation were found in almost every third of the patients (31.4%). Data on blood flow indicators in the uteroplacental circulatory system are presented in table. 4.3.

Table 4.3

Indicators of vascular resistance in the uteroplacental circulatory system in patients of group Ib, (M±m)

Form of disease/indicators		Light (n=4)	Moderate (n=19)	Severe (n=7)	P_1	P_2
Uterine artery on the right	SDR	2,61±0,10	2,92±0,12	3,05±0,15	<0,05	<0,02
	ReI	0,52±0,03	0,61±0,02	0,62±0,03	<0,05	<0,02
	RiI	0,85±0,05	0,97±0,06	1,05±0,04	<0,001	<0,001
Uterine artery on the left	SDR	2,64±0,12	2,94±0,10	3,01±0,04	<0,05	<0,01
	ReI	0,54±0,03	0,64±0,04	0,68±0,04	<0,05	<0,01
	RiI	0,83±0,04	0,98±0,06	1,08±0,05	<0,05	<0,001
Spiral arteries	SDR	1,53±0,09	1,80±0,09	1,83±0,11	<0,05	<0,05
	ReI	0,40±0,02	0,51±0,03	0,58±0,04	<0,01	<0,001

	RiI	0,55±0,03	0,67±0,04	0,68±0,03	<0,02	<0,01

***Note**: P_1 – reliability of differences between patients with mild and moderate degrees, P_2 – reliability of differences between patients with mild and severe degrees.*

Table data 4.3 demonstrate a gradual significant increase in vascular resistance according to the severity of the infectious process. The average indicators of all studied parameters of the uteroplacental circulation in pregnant women with Covid-19 who fell ill in the second trimester of pregnancy were significantly higher than the normative indicators for this period of pregnancy, and in patients with a severe form of the disease - significantly higher compared to women in whom the infectious process in the second trimester of pregnancy was mild.

Data on blood flow in the fetal-placental bed are presented in Table 4.4.

Table 4.4

Indicators of vascular resistance in the vessels of the fetal-placental blood flow in patients of group Ib, (M±m)

Form of disease/indicators		Light (n=4)	Moderate (n=19)	Severe (n=7)	P_1	P_2
Umbilical artery	SDR	3,89±0,22	3,98±0,24	2,32±0,18	>0,5	<0,001
	ReI	0,81±0,05	0,97±0,04	0,56±0,02	<0,02	<0,001
	RiI	1,57±0,08	1,88±0,10	1,15±0,05	<0,02	<0,001
Terminal branches of the umbilical artery	SDR	2,72±0,14	3,19±0,12	3,95±0,15	<0,01	<0,001
	ReI	0,61±0,03	0,80±0,05	0,42±0,02	<0,001	<0,001
	RiI	1,34±0,05	1,59±0,07	0,92±0,04	<0,01	<0,001
Middle cerebral artery	SDR	4,87±0,21	4,95±0,24	1,54±0,09	>0,5	<0,001
	ReI	0,97±0,07	1,00±0,05	0,49±0,03	>0,5	<0,001
	RiI	1,56±0,07	1,71±0,05	0,50±0,03	>0,1	<0,001
Aorta	SDR	6,18±0,22	6,26±0,28	7,89±0,34	>0,5	<0,001
	ReI	1,10±0,03	1,12±0,05	0,72±0,04	>0,5	<0,001
	RiI	1,94±0,09	2,01±0,22	2,41±0,11	>0,5	<0,001

***Note:** P_1 – reliability of differences between patients with mild and moderate degrees, P_2 – reliability of differences between patients with mild and severe degrees.*

Thus, the main hemodynamic changes during Covid-19, concerning the mother-placenta-fetus system in patients of the second trimester, depend not only on

the severity of the viral infection, but also on the compensatory capabilities of the maternal body: the absence or minor changes in the arterial and venous blood flow of the fetus were detected in 54.3% of those examined. In 45.7% of pregnant women, disturbances in the uteroplacental circulation were detected in the second trimester. Combined changes were detected exclusively at the level of intraplacental blood flow - in the terminal branches of the umbilical artery (TBUA) and spiral arteries (SpA). No changes in fetal arterial and venous blood flow were detected. This is evidence of good compensation of the fetoplacental system in the majority of patients infected with SARS-CoV-2.

However, it should be noted that in 16 observations (45.7%) in this group of patients we had profound disorders of the uteroplacental circulation, which led to antenatal fetal death in 5 (14.3%) women, premature birth in 8 (22.9%) and the development of ORP in 4 (11.4%). Antenatal fetal death occurred in women with severe coronavirus infection; in 4 women with a severe form of the disease, the asymmetric form of ORP was diagnosed. Spontaneous preterm birth occurred in another 11.4% of cases. “Premature” maturation of the placenta out of these 16 pregnant women was detected in 8 (50% in relation to the group with a disorder in the mother-placenta-fetus system and 22.9% in relation to all examined in this group) cases. This condition shows that involutive-dystrophic processes occur in the placenta. This was especially pronounced in women with severe COVID-19. During a Doppler examination of pregnant women with severe COVID-19, it was observed that all patients had disorders of the uteroplacental and fetal placental, as well as intraplacental circulation. Hemodynamic disorders of the mother-placenta-fetus system were noted in all 20 women with moderate coronavirus infection in the second trimester. Four women (11.4%) were found to have a critical state of fetal blood flow (Pic. 4.3). Isolated changes in blood flow only in the uterine arteries were found in 3 (8.6%) women with threatened preterm birth.

Picture 4.3. *Doppler metry of uteroplacental circulation. Patient B., 26 years old, 26-27 weeks pregnant, Covid-19, severe form. The critical state of fetal blood flow is the absence of diastole in the umbilical cord artery. PI of the umbilical cord artery - 1.20*

It should be noted that in all 11 cases of severe Covid-19 in the second trimester of pregnancy, there was a violation of venous blood flow. At the same time, changes in hemodynamics occurred in both the fetal and uteroplacental blood flows. With this severity of coronavirus infection, there were signs of a critical state of fetal blood flow (absence of a diastolic component in the blood flow of the umbilical artery), combined disorders in the uterine and umbilical arteries, which led to severe fetal ORP in 4 women. In addition, these same women showed a progressive decrease in the resistance index in the middle cerebral artery, and an increase in resistance in the aorta. We regarded these conditions as progression of centralization of the fetal circulation.

Uteroplacental and fetal-placental circulation in women with Covid-19 in the third trimester of pregnancy.

In the third trimester, the severity of 35 patients was distributed as follows: 7 (20%) women had a mild course of the underlying disease, 21 (60%) patients had a moderate form of the infectious process, and another 7 (20%) had a severe viral

infection. With ultrasound placentography, her premature ripening detected in every third patient of this group (31.4%) (11). Of these observations, antenatal fetal death occurred in 4 (11.4%) women, severe preeclampsia occurred in five cases (14.3%), and pregnancy was complicated by PANLP in another two cases (5.7%). These were mainly patients with severe (7) and moderate (4) forms of the disease. Of these, 6 (54.5%) were found to have polyhydramnios. Severe dystrophic changes in the placenta with cysts, petrification, a decrease in the size of the placenta and the amount of amniotic fluid, as well as diagnosed meconeal fluid, occurred in one woman with a mild course of coronavirus infection during a post-term pregnancy. Thus, the normal echographic structure of the placenta in this group of observations occurred in 65.7% (23) of observations.

When conducting Doppler scanning in 31 patients in the third trimester of pregnancy, we found that with a mild infection, the state of hemodynamics of the uteroplacental and fetal placental blood flow was practically no different from similar indicators in pregnant women without coronavirus infection: uterine artery IR was 0.39±0.14 ($p<0.5$). IR for the umbilical cord artery was 0.51±0.18 ($p<0.02$). The SDR for the umbilical artery was 2.15±0.12 ($p>0.5$). Thus, a mild coronavirus infection when the mother is infected in the third trimester does not affect hemodynamics in the mother-placenta-fetus system.

In moderate to severe cases of the disease, we observed changes in both fetal and uteroplacental blood flow (Tables 4.5, 4.6).

Table 4.5

Indicators of vascular resistance in the vessels of the fetal-placental blood flow in patients of group Ib, (M±m)

Form of disease/indicators		Light (n=7)	Moderate (n=19)	Severe (n=5)	P_1	P_2
Umbilical artery	SDR	3,82±0,2	4,08±0,28	2,28±0,18	>0,5	<0,001
	ReI	0,51±0,18	0,99±0,07	0,59±0,04	<0,02	<0,001
	RiI	1,53±0,04	1,97±0,12	1,95±0,15	<0,02	<0,001
Terminal branches of the umbilical artery	SDR	2, 1±0,18	3,22±0,17	4,05±0,17	<0,01	<0,001
	ReI	0,59±0,05	0,86±0,09	0,92±0,07	<0,001	<0,001
	RiI	1,39±0,02	1,61±0,09	0,99±0,08	<0,01	<0,001

Middle cerebral artery	SDR	4,87±0,21	4,99±0,25	1,56±0,1	>0,5	<0,001
	ReI	0,1±0,02	1,03±0,02	0,49±0,01	>0,5	<0,001
	RiI	1,51±0,09	1,82±0,09	0,46±0,01	>0,1	<0,001
Aorta	SDR	6,2±0,21	6,28±0,31	7,98±0,31	>0,5	<0,001
	ReI	1,11±0,02	1,19±0,04	0,67±0,05	>0,5	<0,001
	RiI	1,96±0,07	2,08±0,28	2,44±0,13	>0,5	<0,001

Note: *P_1 – reliability of differences between patients with mild and moderate degrees, P_2 – reliability of differences between patients with mild and severe degrees.*

Table 4.6.

Indicators of vascular resistance in the uteroplacental circulatory system in patients of group Ib, (M±m)

Form of disease/indicators		Light (n=7)	Moderate (n=19)	Severe (n=5)	P_1	P_2
Uterine artery on the right	SDR	2,63±0,11	3,02±0,14	3,08±0,19	<0,05	<0,02
	ReI	0,41±0,12	0,66±0,01	0,60±0,02	<0,05	<0,02
	RiI	0,87±0,04	0,99±0,05	1,15±0,01	<0,001	<0,001
Uterine artery on the left	SDR	2,62±0,14	2,97±0,11	3,14±0,06	<0,05	<0,01
	ReI	0,54±0,03	0,68±0,02	0,7±0,03	<0,05	<0,01
	RiI	0,80±0,06	1,0±0,02	1,2 ±0,08	<0,05	<0,001
Spiral arteries	SDR	1,55±0,1	1,88±0,1	1,86±0,14	<0,05	<0,05
	ReI	0,42±0,01	0,59±0,07	0,6±0,08	<0,01	<0,001
	RiI	0,57±0,01	0,69±0,03	0,74±0,06	<0,02	<0,01

Note*: P_1 – reliability of differences between patients with mild and moderate degrees, P_2 – reliability of differences between patients with mild and severe degrees.*

Table 4.7.

Correlation matrix of uteroplacental circulation indicators to the severity of covid and the trimester of onset of the disease

r (P<0,05)		Severity of covid	Trimester of the disease
Uterine artery on the right	SDR	0,72	0,73
	ReI	0,71	0,59
	RiI	0,54	0,59
Uterine artery on the left	SDR	0,55	0,61
	ReI	0,54	0,66
	RiI	0,70	0,63
Spiral arteries	SDR	0,74	0,56

	ReI	0,57	0,59
	RiI	0,74	0,55

When analyzing the correlation relationships between the indicators of DPP examination of the fetal-placental and uteroplacental circulation, the severity of Covid-19 and the trimester of onset of the disease, a high and medium strength of positive correlation between these indicators was obtained.

Table 4.8.

Correlation matrix of fetal-placental blood flow indicators to the severity of covid and the trimester of onset of the disease

r (P<0,05)		Severity of covid	Trimester of the disease
Umbilical artery	SDR	0,80	0,81
	ReI	0,79	0,66
	RiI	0,60	0,66
Terminal branches of the umbilical artery	SDR	0,61	0,68
	ReI	0,60	0,73
	RiI	0,78	0,70
Middle cerebral artery	SDR	0,82	0,62
	ReI	0,63	0,65
	RiI	0,82	0,61
Aorta	SDR	0,73	0,75
	ReI	0,61	0,82
	RiI	0,77	0,61

Thus, changes in hemodynamics in the mother-placenta-fetus system had a direct correlation with the severity of the underlying disease (from r+0.6 to +0.82, p <0.05). In the hemostasis system, there was also a shift towards increased coagulation, which correlated with the severity of the disease and was a reflection of endothelial dysfunction (r+0.58, 0.75, 0.86, p<0.05).

Thus, despite the fact that in 65.7% of cases we had an echographically normal structure of the placenta when infected with Covid-19 in the third trimester of pregnancy, however, Dopplerography of these patients indicated significant disturbances in the fetal and uteroplacental circulation, which progressed as the general condition of the patients worsened, especially in two women with

community-acquired pneumonia. As a result, only 15 (50%) were delivered at 37-38 weeks. Caesarean section occurred in 74.3% of this group, in 26 women.

4.2. The state of the hemostatic system in pregnant women with respiratory viral infections

Covid-19 is a risk factor for thromboembolic complications during pregnancy and after delivery. We examined the state of the hemostatic system in 105 pregnant women with Covid-19 and in 50 pregnant women in the control group. The following parameters were determined: INR, D-dimer, APTT, platelet count and their aggregation function, fibrinogen. The frequency of tests depended on the severity of the patients' condition. At the very beginning of the disease, a coagulation disorder associated with the introduction of the virus; we did not observe signs of disseminated intravascular coagulation syndrome, but hypercoagulation occurred. This is evidenced by a sharp increase D-dimer, moderate decrease in platelet count, prolongation of prothrombin time, increase in fibrinogen levels (response to the acute phase of inflammation), the activity of antithrombin III did not decrease, i.e. there is no microangiopathy and we can't even talk about DIC syndrome. However, as the disease progresses, hypercoagulation increases and signs of intravascular coagulation appear.

In accordance with the goals and objectives of the study, we determined the state of the hemostatic system in pregnant women with coronavirus infection, which manifested itself in different trimesters of pregnancy.

The state of the hemostatic system in pregnant women with a mild form of coronavirus infection.

A study of the hemostasis system was carried out in 19 patients with a mild form of Covid-19. (tab. 4.9 and 4.10).

Table 4.9

State of the hemostatic system in pregnant women with mild disease, (M±m)

Indicators	Control group (n=50)	Pregnant women with mild COVID-19 (n=19)	P
Lee-White clotting time (min)	7,2±0,3	7,8±0,4	>0,2
INR	0,90±0,04	0,95±0,02	>0,2
Fibrinogen concentration (g/l)	4,6±0,2	4,9±0,2	>0,2
APTT (sec)	17,1±0,6	24,9±0,9	**<0,001**
Platelet count (1x109/l)	221,7±3,4	180,5±6,5	**<0,001**
Platelet aggregation (stimulation of ADP 1x10-3 M Tma%)	40,2±1,4	42,1±1,5	>0,5
D-dimer (ng/ml)	421,3±5,7	571,9±20,4	**<0,001**
Prothrombin time	10,3±0,4	14,8±0,5	**<0,001**
Antithrombin III activity (%)	89,6±3,1	93,0±3,3	>0,5

Note: *P – significance of differences in the compared indicators with the group of pregnant women without Covid-19*

Table 4.10

Comparative characteristics of coagulogram in healthy patients and pregnant women with mild Covid-19

Indicators	Healthy pregnant women n=50 (abs.)	Pregnant women with mild COVID-19 n=19 (abs.)	χ^2	P	OR	DI min	DI max
Clotting time (m) Up to 6 minutes	17	4	1,090	0,296	0,52	0,15	1,80
6 or more minutes	33	15	1,090	0,296	1,93	0,55	6,73
INR to 1	27	9	0,243	0,622	0,77	0,27	2,21
1 or more	23	10	0,243	0,622	1,30	0,45	3,76
Fibrinogen concentration (g/l) to 5	32	9	1,579	0,209	0,51	0,17	1,48
5 or more	18	10	1,579	0,209	1,98	0,68	5,76
APTT (sec) Until 20	38	1	28,034	0,0001	0,02	0,00	0,15
20 or more	12	18	28,034	0,0001	57,00	6,87	472,84

Platelet count($1x10^9$/l) Less than 200	14	14	11,917	0,001	7,20	2,18	23,74
200 or more	36	5	11,917	0,001	0,14	0,04	0,46
Platelet aggregation%) Until 30	11	0	4,973	0,026	0,00	-	-
30 or more	39	19	4,973	0,026	-	-	-
D-dimer up to 450	35	0	26,991	0,0001	0,00	-	-
450 or more	15	19	26,991	0,0001	-	-	-
Prothrombin time less than 9	19	0	9,964	0,002	0,00	-	-
9 or more	31	19	9,964	0,002	-	-	-

As can be seen from tables 4.9 and 4.10, in pregnant women with a mild form Covid-19 On average, hemostasis indices for the main parameters did not differ significantly from the control group. But at the same time, it should be noted that such indicators as APTT (characteristic of the internal pathway of blood coagulation, the time during which a clot forms, i.e. this is a method that evaluates the time of influence of plasma coagulation factors on the formation of a blood clot), the total number of platelets, D-dimer (fibrin/fibrinogen breakdown, indicating a tendency to thrombosis), prothrombin time (time of formation of a vascular thrombus) had significant differences in side increase compared to pregnant women from the control group. Thus, even with a mild degree of coronavirus infection, pregnant women have a risk of increased thrombus formation, which requires appropriate correction. Particularly noteworthy is the fact of a significant decrease in platelet levels in pregnant women with a mild form of coronavirus infection, however, the numbers did not go beyond the reference values.

Table 4.11

State of the hemostatic system in pregnant women with a moderate form of the disease, (M±m)

Indicators	Control group (n=50)	Pregnant women with moderately severe form (n=61)	P
Clotting time (min)	7,2±0,3	6,0±0,2	<0,01
INR	0,90±0,04	1,64±0,06	<0,001

Fibrinogen concentration (g/l)	4,6±0,2	4,3±0,2	>0,5
APTT (sec)	17,1±0,5	19,1±0,7	<0,01
Platelet count (1x109/l)	220,6±5,8	152,6±6,1	<0,001
Platelet aggregation (ADP stimulation 1x10-3 M Tma%)	40,2±1,4	38,0±1,4	>0,2
D-dimer	423,2±11,1	990,9±16,8	<0,001
Prothrombin time	10,3±0,4	6,6±0,2	<0,001

Note: *P – reliability of differences in the compared indicators with the control group.*

The state of the hemostatic system in pregnant women with a moderate form of coronavirus infection. A study of the hemostasis system was carried out in 61 patients with a moderate form of Covid-19. (Tables 4.11 and 4.12).

Table 4.12

Comparative characteristics of the coagulogram of healthy patients and pregnant women with moderate disease.

Indicators	Healthy pregnant women n=50 (abs.)	Pregnant women with moderate weight. shape n=61 (abs.)	χ^2	P	OR	DI min	DI max
Clotting time (m) Up to 6 minutes	17	28	1,615	0,204	1,65	0,76	3,56
6 or more minutes	33	33	1,615	0,204	0,61	0,28	1,31
INR to 1	27	4	30,726	0,000	0,06	0,02	0,19
1 or more	23	57	30,726	0,000	16,73	5,26	53,17
Fibrinogen concentration (g/l) to 5	32	40	0,030	0,863	1,07	0,49	2,34
5 or more	18	21	0,030	0,863	0,93	0,43	2,04
APTT (sec) Until 20	38	33	5,718	0,017	0,37	0,16	0,85
20 or more	12	28	5,718	0,017	2,69	1,18	6,11
Platelet count($1x10^9$/l) Less than 200	14	49	30,655	0,000	10,50	4,34	25,39
200 or more	36	12	30,655	0,000	0,10	0,04	0,23

Platelet aggregation (%) Until 30	11	18	0,803	0,370	1,48	0,62	3,53
30 or more	39	43	0,803	0,370	0,67	0,28	1,60
D-dimer up to 450	35	0	62,364	0,000	0,00	-	-
450 or more	15	61	62,364	0,000	-	-	-
Prothrombin time less than 9	19	52	26,609	0,000	9,43	3,80	23,40
9 or more	31	9	26,609	0,000	0,11	0,04	0,26

In the group of patients with a moderate form, we have a significant increase in aPTT, which represents a risk of bleeding during childbirth or after childbirth and indicates a low coagulation potential of the blood. At the same time, a significant increase in D-dimer and INR indicates an active process of thrombus formation in pregnant women with coronavirus infection. At the same time, we have a significant decrease in clotting time, which can be regarded as the hypercoagulable stage of DIC syndrome. A significant amount of soluble fibrin monomer complexes appears in the blood of pregnant women with a moderate form of coronavirus infection. This indicates a risk of already developed thrombophilia, a sharp deterioration in the function of the hemostatic system, i.e. these patients have developed complexes associated with impaired fibrinolysis and have a high risk of thrombus formation.

Table 4.13

Main parameters of the hemostatic system in pregnant women with severe disease, (M±m)

Indicators	Control group, (n=50)	Pregnant women with severe form, (n=25)	P
Clotting time (sec)	7,2±0,3	5,0±0,2	<0,001
INR	0,90±0,04	2,02±0,05	<0,001
Fibrinogen concentration (g/l)	4,6±0,2	5,9±0,3	<0,001
APTT (sec)	17,1±0,5	22,1±0,7	<0,001
Platelet count (1x109/l)	220,6±5,8	152,7±4,8	<0,001
Platelet aggregation (stimulation by ADP1x10-3 M Tma%)	40,2±1,4	33,9±0,9	<0,001
D-dimer	423,2±11,1	1347,2±42,2	<0,001

Prothrombin time	10,3±0,4	5,8±0,3	<0,001

Note: *P – reliability of differences in the compared indicators with the control group;*

The state of the hemostasis system in pregnant women with severe coronavirus infection. A study of the hemostasis system was carried out in 25 patients with severe COVID-19 (Tables 4.13 and 4.14).

Table 4.14

Comparative characteristics of the coagulogram in healthy patients and pregnant women with severe disease.

Indicators	Healthy pregnant women n=50 (abs.)	Pregnant women with severe form n=25 (abs.)	χ^2	P	OR	DI min	DI max
Clotting time (m) Up to 6 minutes	17	19	11,779	0,001	6,15	2,07	18,26
6 or more minutes	33	6	11,779	0,001	0,16	0,05	0,48
INR to 1	27	0	21,094	0,000	0,00	-	-
1 or more	23	25	21,094	0,000	-	-	-
Fibrinogen concentration (g/l) to 5	32	9	5,273	0,022	0,32	0,12	0,86
5 or more	18	16	5,273	0,022	3,16	1,16	8,59
APTT (sec) Until 20	38	9	11,398	0,001	0,18	0,06	0,50
20 or more	12	16	11,398	0,001	5,63	1,98	15,98
Platelet count ($1x10^9$/l) Less than 200	14	25	34,615	0,000	-	-	-
200 or more	36	0	34,615	0,000	0,00	-	-
Platelet aggregation (%) Until 30	11	6	0,038	0,845	1,12	0,36	3,49
30 or more	39	19	0,038	0,845	0,89	0,29	2,78
D-dimer up to 450	35	0	32,813	0,000	0,00	-	-
450 or more	15	25	32,813	0,000	-	-	-
Prothrombin time less than 9	19	25	26,420	0,000	-	-	-
9 or more	31	0	26,420	0,000	0,00	-	-

All indicators of the hemostatic system in pregnant women with severe forms were significantly worse compared to women in the control group and two other comparison groups. They indicated obvious thrombophilia, which is confirmed by the clinical course of the disease - severe pneumonia, PANLP. All patients in this group underwent emergency delivery using nonspecific methods of thrombosis prevention. After delivery, direct anticoagulants - low molecular weight heparins - were prescribed.

Table 4.15.

Correlation matrix of hemostasis indicators to the severity of Covid-19 and the trimester of onset of the disease

r (P<0,05)	Heaviness Covid-19	Trimester of disease onset
Clotting time (min)	-0,68	-0,62
INR	0,75	0,72
Fibrinogen concentration (g/l)	0,58	0,62
APTT (sec)	-0,72	-0,74
Platelet count ($1x10^9$ /l)	-0,58	-0,59
Platelet aggregation	-0,71	-0,62
D-dimer	0,86	0,8
Prothrombin time	-0,71	-0,75

When analyzing the correlation relationships between the indicators of the hemostatic system, the severity of Covid-19 and the trimester of onset of the disease, data were obtained indicating the presence of a relationship between the compared indicators. Thus, an average strength of negative correlation was noted between clotting time indicators, platelet count and the severity of Covid-19 and the trimester of onset of the disease (Table 6). There was a shift in the hemostasis system towards increased coagulation, which correlated with the severity of the disease and was a reflection of endothelial dysfunction.

4.3. Endothelin-1 in pregnant women of the main and control groups

The study was carried out on 19 patients with a mild form of Covid-19, in 61 patients with moderate-severe and 25 patients with severe form Covid-19 as well as in 50 pregnant women in the control group (Table 4.16).

Table 4.16

Endothelin-1 in pregnant women of the main and control groups (reference values – 0.1-1.0 fmol/ml; P)

Groups/indicators	Endothelin – 1 (fmol/ml)	P
Control group (n=50)	0,86 ±1,14	>0,5
Pregnant women with mild course (n=19)	0,94±0, 2	>0,5
Pregnant women with moderate course (n=61)	2,5±1,1	<0,001
Pregnant women with severe disease (n=25)	4,2±0,8	<0,001

Note: *P – reliability of differences in the compared indicators of the control group with pregnant women of the main group*

When studying the concentration of endothelin-1 in pregnant women in the control group, no significant differences were revealed in comparison with the reference values. When comparing data obtained from pregnant women with mild cases and pregnant women without coronavirus infection, we also did not obtain significant differences ($p>0.5$). This indicates a low vasoconstrictor potential of the blood in pregnant women with mild coronavirus infection.

Table 4.16 indicate that there are significant differences in the concentration of endothelin-1 in the groups of patients with moderate and severe forms compared to the control group ($p<0.001$). Apparently, this can explain the long-term and more severe changes in the utero- and fetal-placental circulation in patients with moderate to severe disease. This can also explain the frequency of severe preeclampsia, PANLP, antenatal fetal death, as well as premature placental maturation in 22 (21%) patients with severe COVID-19.

Table 4.17.

Correlation matrix of indicators of endothelial condition to severity and trimester of onset of the disease

	Heaviness Covid-19	Trimester of the disease
ET-1, fmol/ml,	-0,78	-0,72

Changes in hemodynamics in the mother-placenta-fetus system had a direct correlation with the severity of the underlying disease. This is reflected by the high strength of the negative correlation between Endothelin-1 and the severity of Covid-19, the trimester of onset of the disease

4.4. Morphological structure of the placenta

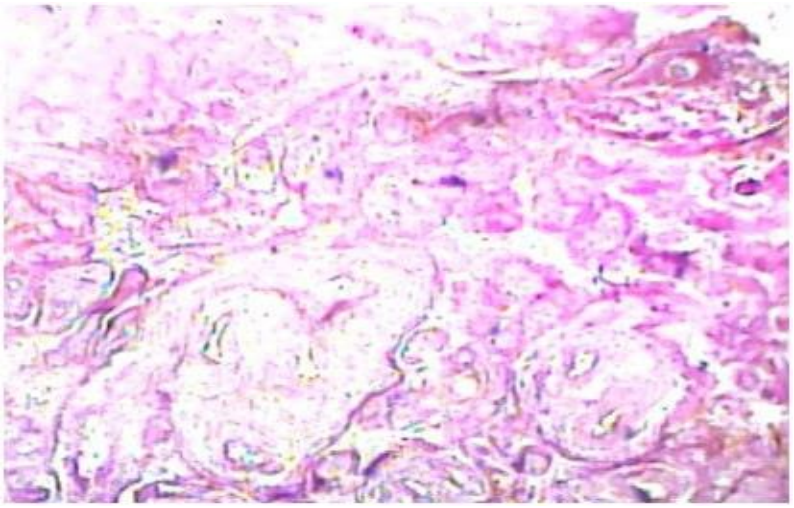
In order to study the effect of coronavirus infection on the condition of the placenta, macroscopic and microscopic examination of placentas/abortive material was carried out in all examined women.

According to the timing of the infection, the patients were divided into 35 women in the first, second and third trimesters. During full-term pregnancy (37-42 weeks), 62 (59%) women gave birth. In the period from 24 to 37 weeks, 24 (22.9%) patients gave birth. In another 19 (18%) the pregnancy was terminated before 22 weeks.

Separately, it should be noted the results of a histological examination of the contents of the uterine cavity in patients with a gestation period of up to 22 weeks. Due to NB and spontaneous abortion, 14 evacuation of contents from the uterine cavity were performed. At the request of the woman, in connection with the diagnosed Covid-19, 5 artificial terminations of pregnancy were carried out in terms of up to 12 weeks. When comparing histological data obtained during artificial termination of pregnancy with abortive materials obtained from healthy women, we did not find significant differences. It should be noted that in patients with Covid-19, in some cases (2 out of 5 = 40%), we found swelling of the intervillous space, which apparently indicates an additional load on the developing uteroplacental blood flow in these women.

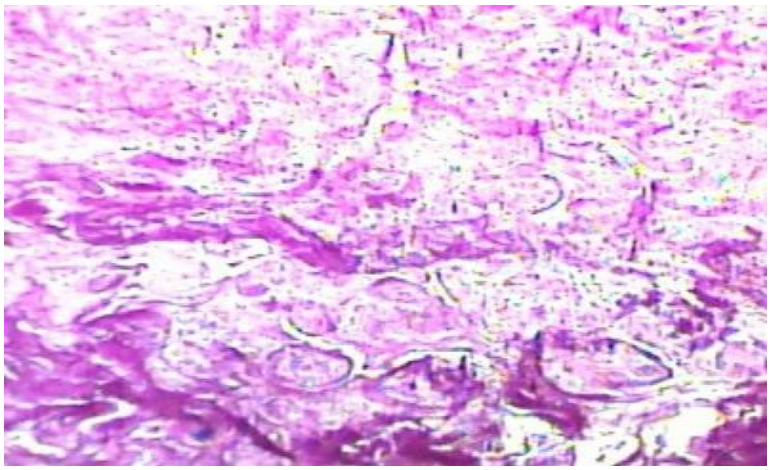
However, analysis of histological examination of UP and spontaneous abortion showed the development of primary placental insufficiency in these

patients. This was manifested by a violation of the development of the villous chorion - there was no vascularization and growth. Stromal edema, reduction of villi and a large number of avascular villi, their sclerosis, thinning of the trophoblast, as well as thrombosis of the intervillous space became a distinctive characteristic of this material (Pic. 4.4).



Picture 4.4. Impaired vascularization and sclerosis of the chorionic villi, stromal edema, thinning of the trophoblast of the developing placenta of patient A., 20 years old. Covid-19, moderate course, non-developing pregnancy 7-8 weeks. Hematoxylin and eosin staining. Ok.10. Ob.10.

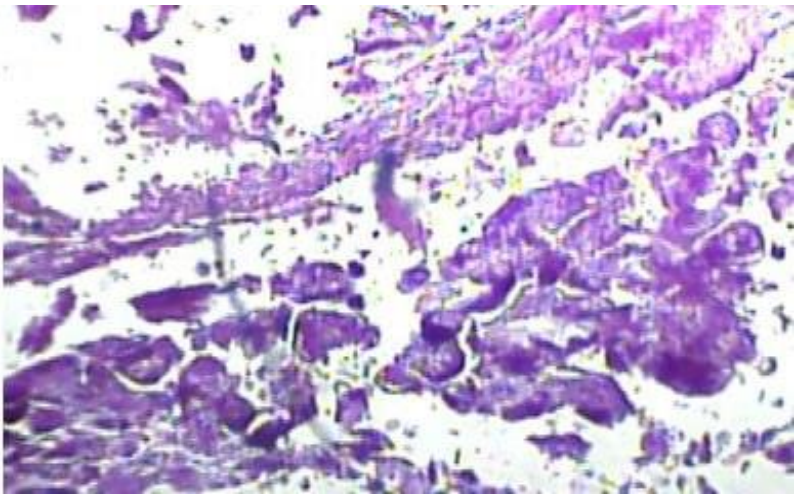
During a histological examination of the material obtained during spontaneous abortion, we had small groups of villi with necrosis of trophoblasts, fibrin deposition, which indicates processes of impaired vascularization of the chorion. Apparently, these manifestations of primary placental insufficiency were the cause of spontaneous abortion in the examined patients. In Pic. 4.5. presents a histological picture obtained during the evacuation of the contents of the uterine cavity in a patient during a spontaneous abortion, which occurred 2 weeks after suffering from early COVID-19.



Picture 4.5. Trophoblast necrosis, fibrin deposition, impaired vascularization of the chorionic villi of the developing placenta of patient V., 37 years old. Pregnancy 10-11 weeks. Spontaneous incomplete miscarriage. Condition after suffering from Covid-19. Hematoxylin – eosin staining. Ok.10. Ob.10.

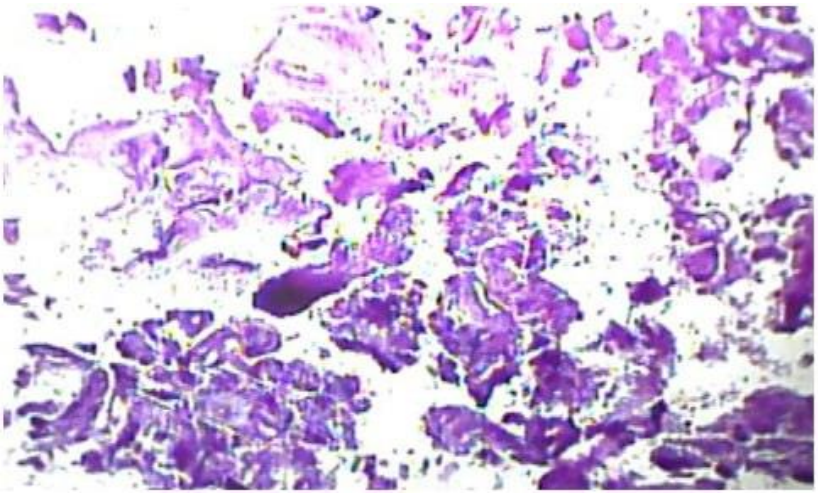
Separately, attention should be paid to swelling and focal hemorrhages found in the endometrium of patients with spontaneous abortion/UP (in 6 women - 42.9%), necrotic foci of the endometrium (in 4 women - 28.6%) and leukocyte infiltration (in 4 women - 28.6%). Thus, in all patients of this group, when examining the endometrium, histological signs of chronic endometritis were also revealed, which could serve as a premorbid background for termination of pregnancy in women with Covid-19. The results of the morphological study of the obtained material correlate with the data obtained from ultrasound of these patients.

A morphological study of the patients' placentas showed that in all cases, regardless of the gestational age, when birth occurred in the acute period of the disease (28 patients - 26.7%), there were signs of acute nonspecific inflammation in the placenta, the main symptom of which was the infiltration of polymorphonuclear leukocytes in the intervillous space (Pic. 4.6).



Picture. 4.6. Infiltration of polymorphonuclear leukocytes – neutrophils into the intervillous space of the placenta of patient R., 23 years old. Pregnancy III, 38-39 weeks. Childbirth III. Covid-19, mild acute. Hematoxylin-eosin staining. Ok. 10. Ob. 10.

Particularly noteworthy is the histological structure of the placentas of patients after suffering from Covid-19. A total of 46 placentas were studied (20 from preterm birth and 26 from term birth).

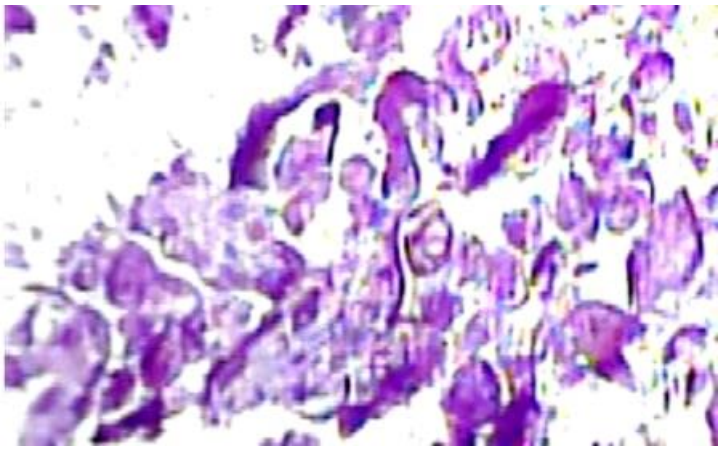


Picture 4.7. Infiltration of plasma cells, lymphocytic focal lesions of the villi (signs of chronic inflammation of the decidua) of the placenta of patient R., 21 years old. Pregnancy I. 39-40 weeks. Urgent birth. She suffered Covid-19 at 25-26 weeks of pregnancy. Hematoxylin – eosin staining. Ok.10. Ob.10.

Common to all these studies was the presence of signs of chronic inflammation (31 - 67.4%), which were manifested, by infiltration of plasma cells,

signs of chronic inflammation of the decidua and lymphocytic focal lesions of the villi (Pic. 4.7).

In 18 patients (39.1%), who were delivered after recovery from Covid-19 (time after recovery was from 4 to 33 weeks), an increased number of capillaries was found in the terminal villi (Pic. 4.8). This indicates a decrease in maternal blood oxygen saturation, which persisted until delivery, despite the mother's clinical recovery.

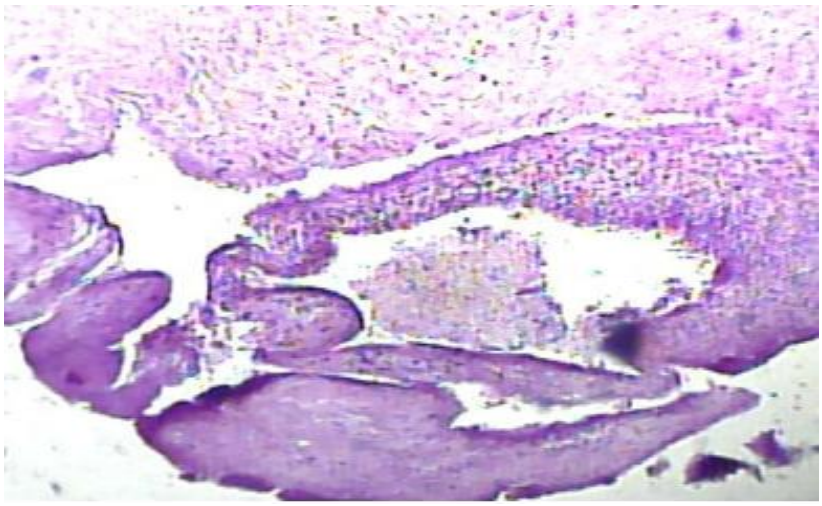


Picture 4.8. Increased number of capillaries in the terminal villi of the placenta of patient V., 30 years old. Pregnancy II. 39-40 weeks Urgent birth. Covid-19 was 22-23 weeks pregnant. Hematoxylin-eosin staining. Ok.10. Ob.20.

Thus, we can say that in patients who have suffered an acute coronavirus infection, the morphological changes in the placenta, and therefore in the uteroplacental circulation, are stable.

We found histological changes not only in the maternal-fetal circulation, but also in the fetal-placental circulation. These changes concerned mainly vascular malperfusion: hypertrophy of membrane arterioles, infarctions, fibrinoid necrosis. In case of PANLP and antenatal fetal death, histological examination of the placenta revealed edema and retroplacental hematoma, subchorionitis (Pic. 4.9). Noteworthy is the large number of blood clots in the intervillous space, which are of embryonic origin. These data are consistent with the data presented in the work of Y.Y. Zhou et al. (2020), which also indicates that 85% of blood clots in the intervillous space are of fetal origin. These conditions further support the theory of Covid-19

pathogenesis associated with vasculopathy and hypercoagulability. Thus, we consider these changes in the placenta as a response to a viral infection. We found more serious changes in the placenta with antenatal fetal death, as well as with a combination of coronavirus infection with pre-eclampsia and PANLP. In this regard, we see a valid theory of the development of pre-eclampsia and PANLP as a violation of vascularization and endothelial dysfunction.



Rice. 4.9. Edema and retroplacental hematoma, subchorionitis of the placenta of patient G., 26 years old. Pregnancy IV. 29-30 weeks Covid-19, moderate. PANLP. Antenatal fetal death. Hematoxylin-eosin staining. Ok.10. Ob. 20.

We noted the absence of significant changes in the placenta in patients who suffered a coronavirus infection in the third trimester, especially on the eve of childbirth, although the clinical manifestation of the covid process in this group of patients was more pronounced. From this it follows that with increasing gestational age, the barrier function of the formed placenta is expressed in a more compensated role.

Thus, we did not find any specific symptoms of placental damage due to coronavirus infection. The existing changes indicate the systemic influence of this viral infection on the entire mother's body, including the utero- and fetal-placental circulation. More profound changes occurred with the development of pregnancy complications such as pre-eclampsia, PANLP, and antenatal fetal death. The severity of histological changes in the placenta also depended on the stage of pregnancy in

which the patient suffered coronavirus infection - the earlier, the more serious the changes. When the mother was infected in the third trimester of pregnancy, the histological structures of the placentas were practically no different from those obtained from healthy mothers.

To illustrate this section of the work, we provide the following clinical example:

Patient M., born in 1996 from Samarkand, was admitted to the Regional Perinatal Center with complaints of cough, fever up to 39^0 C, headaches, weakness, fatigue, tinnitus, bleeding from the genital tract.

Complete blood count: Hb-81 g/l; Red blood cells - 2.9; CPU-0.7; Platelets - 168.0; Leukocytes-7.3; p/i-5%; s/ya-65%; monocytes-4%; lymphocytes - 26%; ESR-18 mm/h.

Biochemical blood test: Total protein-64; Glucose-3.8; Urea-6.9; Residual nitrogen - 21.9; Creatinine-83.2. Total bilirubin - 14.6; AlT-0.70; AsT-0.50.

Coagulogram: PTV-13sec; PTI-112%; INR-1.25; D-dimer-1.5; Hematocrit-35%; APTT-27sec; fibrinogen-3.6; CRP-48.

Endothelin-1 – 2.15.

Ultrasound: Pregnancy 28-29 weeks. Abruption of a normally located placenta. Antenatal fetal death.

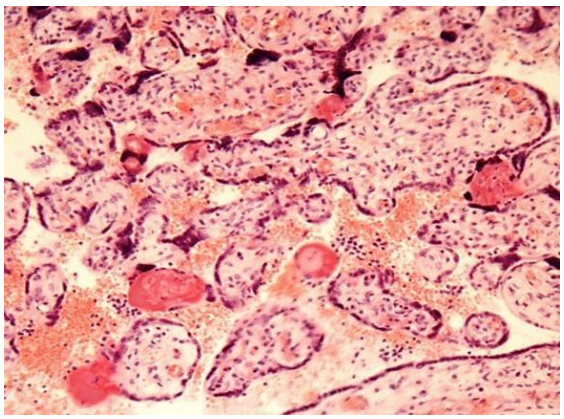
The diagnosis was made upon admission: Pregnancy I. Weeks 28. Childbirth I. Progressive abruption of a normally located placenta. Antenatal fetal death. Preeclampsia is severe. Chronic pyelonephritis. COVID-19. Community-acquired pneumonia.

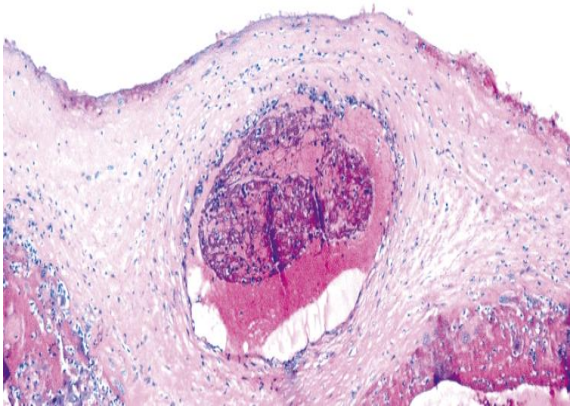
The operation was performed: Emergency lower-median laparotomy. Caesarean section in the lower uterine segment.

During the operation, Cuveler's uterus, hemorrhages and hematomas were discovered in the uterine appendages and ovaries. During the operation, it was decided to perform extirpation of the uterus and appendages.

The patient received antibiotic therapy (Cefepime 1.0 x 2 times a day), antiplatelet therapy - LMWH (Clexane 0.6 mg/day x 2 times a day); crystalloid and colloid solutions, drugs supporting the cardiovascular system.

With improvement in general condition, the patient was discharged and further rehabilitation was prescribed.





A morphological study of the tissue of the removed uterus and placenta was carried out: a histological picture of hemorrhages in the uterine wall with vascular malformations, thrombosed large and small vessels are visible, on the placental tissue there are chorionic villi with hemorrhages and fibrinoid necrosis, in places infiltration of neutrophils in the intervillous space is visible.

CONCLUSION ON CHAPTER IV

Our studies have shown that viral infection in pregnant women leads to significant activation of the hemostatic system (different from physiological changes in this system that occur during pregnancy). The degree of activation depends on the severity of the viral disease, the addition of obstetric pathology (preeclampsia, PANLP, premature birth, UP, etc.), and the presence of concomitant somatic pathology. Coronavirus infection leads to the intravascular formation of increased, concentrations of soluble and insoluble fibrin, a decrease in the number of platelets with an increase in their aggregation function, i.e. conditions are created for increased thrombus formation, which is clinically manifested by the development of severe pneumonia (in 5 - 4.8% of pregnant women), respiratory failure (in 2 - 1.9% of pregnant women), PANLP (in 4 - 3.8% of pregnant women), and antenatal fetal death (in 9 - 8.6% of pregnant women). It should be noted that complications of Covid-19 that vary in clinical course (bleeding after childbirth or thrombosis of the vascular bed) cause an almost identical intensification of thrombus formation. This once again confirms the nonspecificity of hemostasis disorders in Covid-19 under the influence of various causal causes.

Due to the fact that in 82.9% (87) of pregnant women we found changes in hemodynamics in the utero- and fetal-placental circulation, to improve perinatal outcomes and the risks of additional pregnancy complications in women with Covid-19, it is also necessary to prescribe drugs to improve blood flow in the “mother-placenta-fetus” system.

Our study is a definite stage in the further development of the problem of thrombotic complications in obstetrics, and can also serve as the basis in the future for the empirical prescription of drugs that affect hemodynamics in the mother-placenta-fetus system during seasonal viral infections.

CHAPTER V. IMPROVING TACTICS OF MANAGEMENT OF PREGNANT WOMEN WITH RESPIRATORY VIRAL INFECTIONS

5.1. Factors influencing improved perinatal outcomes

Based on the data obtained on the state of the hemostatic system in pregnant women with COVID-19, as well as in order to improve perinatal outcomes, we substantiated and assessed the clinical and laboratory effectiveness of preventive measures aimed at reducing the severity of thrombophilic conditions, both during pregnancy and after delivery.

In pregnant women with a mild form of the disease during premature pregnancy and when deciding to prolong pregnancy, nonspecific methods were prescribed aimed at normalizing hemodynamics, especially in the microvasculature, correcting disturbances in water-salt balance, the function of the cardiovascular and respiratory systems, as well as preventing placental insufficiency. For this purpose, dipyridamole was prescribed (from the second trimester!) at 75 mg/day for a long time, 4-6 weeks. The prescription of dipyridamole is also justified from the point of view of its vasodilating and angioprotective properties, as well as to improve platelet function and erythrocyte plasticity. The dose was adjusted or the drug was discontinued after studying the coagulogram.

To normalize the function of the vascular endothelium, prevent the formation of blood clots, regulate vascular tone, blood flow and tissue perfusion (especially in the placenta), a nitric oxide donor was prescribed - Tivortin 100 mg intravenously No. 7 in the hospital, or 2 scoops with meals 3-4 times a day after discharge / outpatient, long-term, in courses of 2 weeks.

However, these measures are not sufficient for moderate and severe forms of coronavirus infection in pregnant women. In this regard, we have developed and carried out specific prevention of thrombotic complications and improvement of blood circulation in the microcirculation system of vital organs by prescribing LMWH - clexane 0.4-1.0 mg/day x 2 times a day (depending on the severity of the

condition, gestational age, weight of the patient and data of the hemostasis system). The drug was not prescribed in case of emergency delivery. The drug was discontinued 8 hours before planned delivery and re-administered 8 hours after delivery. An objective criterion for the effectiveness of specific preventive measures was the absence of obvious signs of thrombosis in 70% of patients after delivery, as well as a more rapid restoration of the normal functioning of the hemostatic system in these women. The use of low molecular weight heparin (LMWH) was evaluated in 40 pregnant women with coronavirus infection. The inclusion of these patients in this group is due to a number of reasons:

1) The presence of an obvious thrombophilic state both before and after delivery

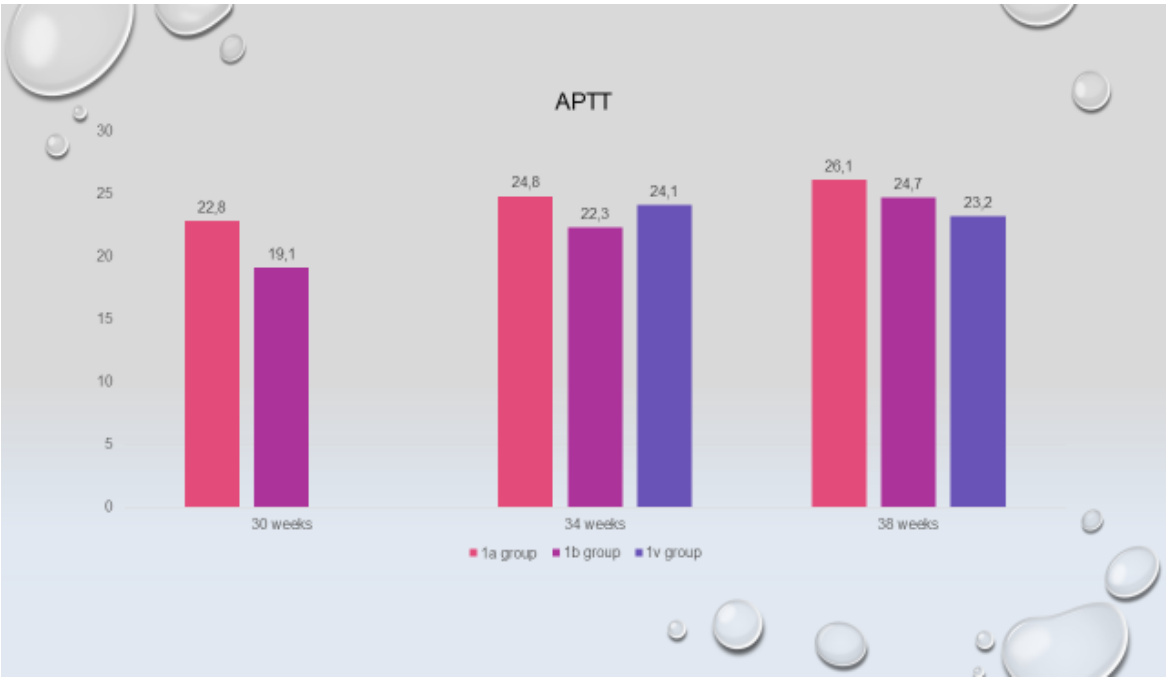
2) Comparative prevalence of moderate and severe forms of COVID-19 among pregnant women

3) An attempt to show the safety of using LMWH in pregnant women with COVID-19

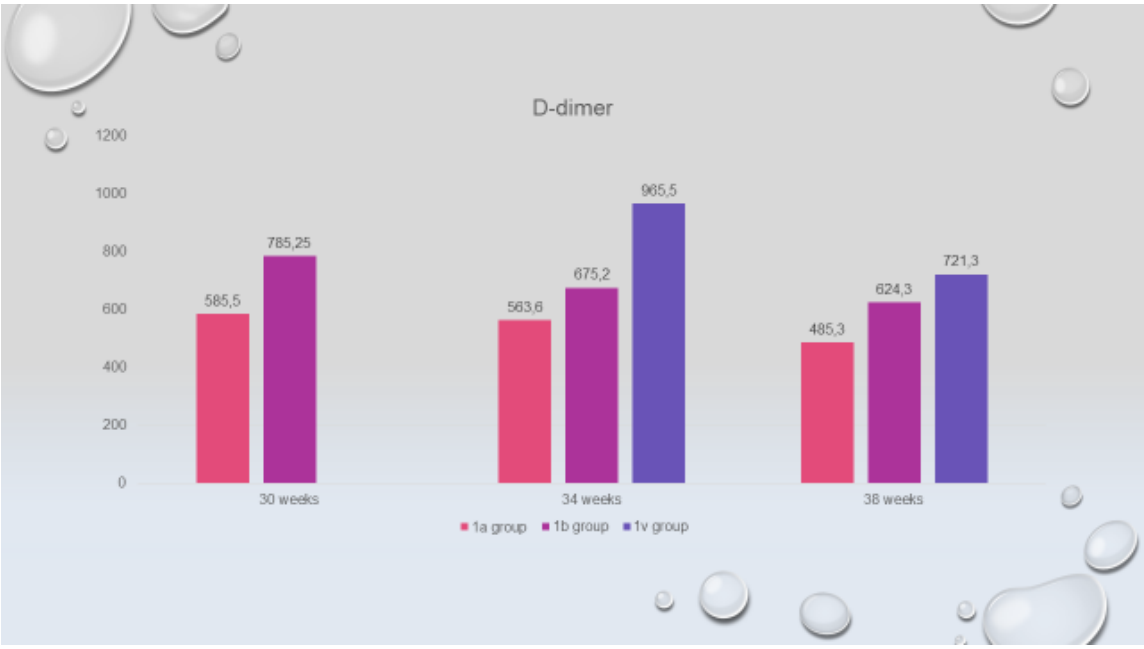
4) Obtain evidence of the need to follow recommendations for the treatment of patients with COVID-19

After discharge, a prophylactic dose of 0.4-0.6 mg/day was prescribed for 4-6 weeks. After the end of the postpartum period, the function of the hemostatic system was re-monitored and, depending on the indicators, the patient was transferred under the supervision of a local doctor. We did not observe any complications associated with the use of Clexane.

Analysis of the results of a study of the hemostasis system in this group of patients showed that under the influence of LMWH after delivery, there was a normalization of indicators characterizing the total activity of blood coagulation factors - APTT, by 10-13 days after delivery (Pic. 5.1)



Picture 5.1. *APTT indicators at 30-34-38 weeks of pregnancy*



Picture 5.2. *D-dimer indicators 30-34-38 weeks of pregnancy*

An important characteristic of the restoration and normalization of hemostasis in pregnant women with Covid-19 and the risk of thrombotic complications after delivery was the concentration of D-dimer, which in all groups examined significantly decreased within the first 14 days after birth, but did not reach normal values (Pic. 5.2).

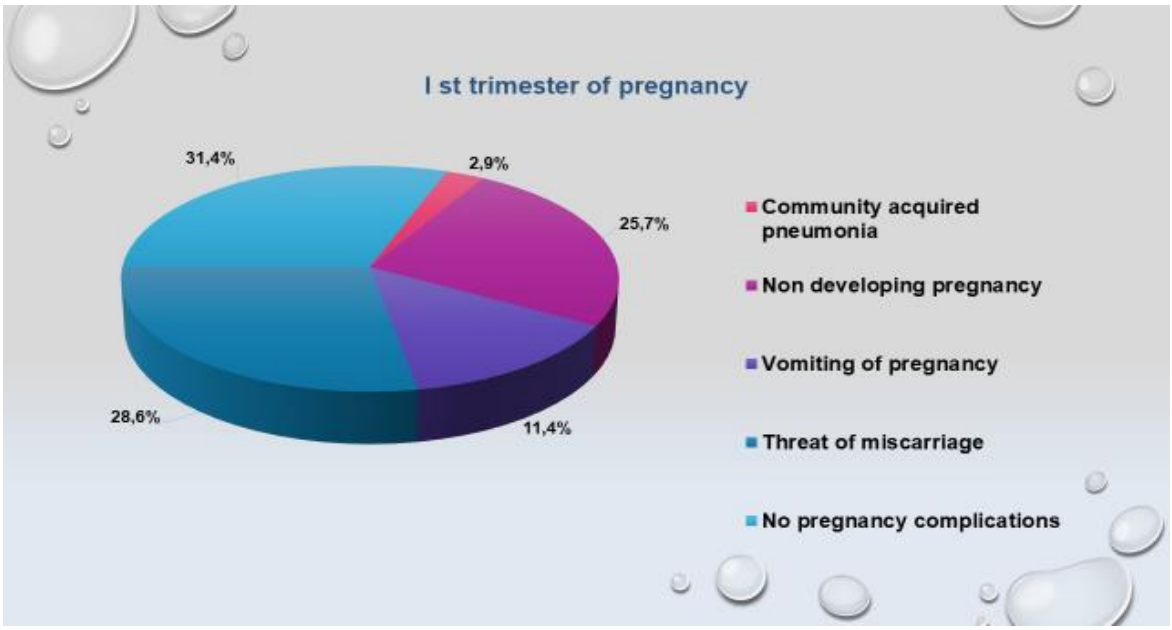
After recovery and discharge from the hospital, patients are prescribed long-term thromboprophylaxis by prescribing prophylactic doses of LMWH. In this case, one should take into account the duration of pregnancy, the presence of other risk factors (somatic pathology, preeclampsia, PANLP, planned cesarean section, etc.), the choice of method, time and place of delivery.

A.I. Vorobiev et al., (2016) [9], and even earlier A.P. Momot et al., (2011) [30] described a tendency to thrombosis, confirmed laboratory, but without clinical manifestations. This condition is called hypercoagulability syndrome in the literature. It manifests itself especially often with endothelial dysfunction. Considering that in our studies at previous stages we found signs of endothelial dysfunction in pregnant women with COVID-19, after discharge from the hospital (regardless of whether the pregnancy was maintained or not), in order to correct the identified changes, we monitored the coagulation properties of the blood.

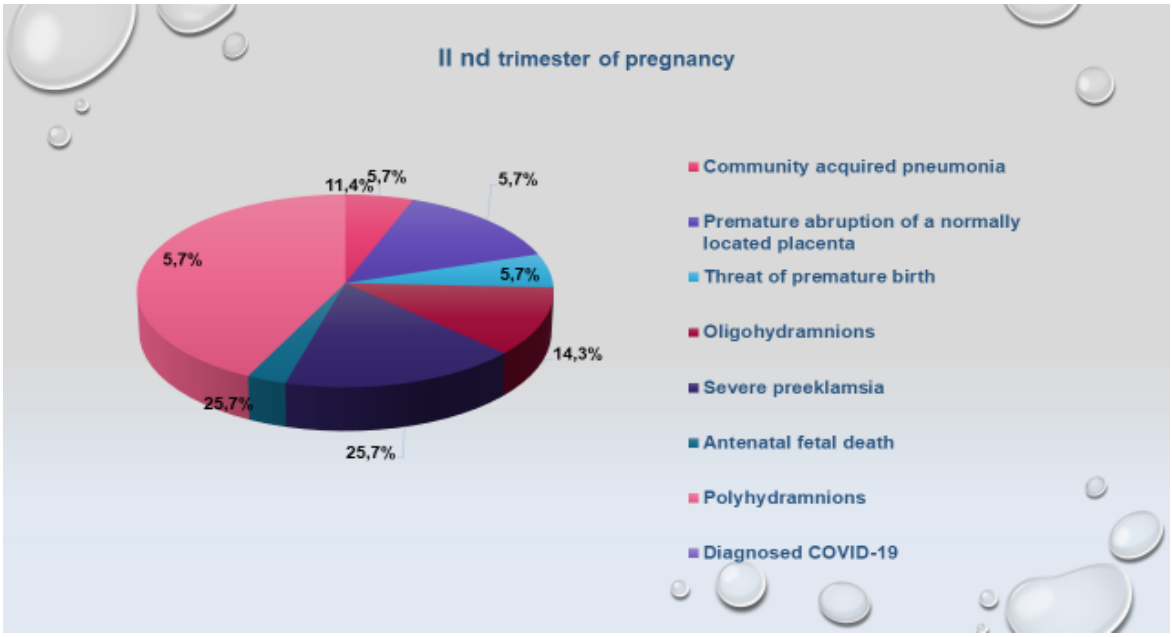
When thrombotic readiness was detected, especially when other risk factors were added (obesity, arterial hypertension, high parity, a history of cesarean section, planned CS, pregnancy complications, etc.), we carried out primary and secondary thromboprophylaxis. Of course, these measures were combined with treatment of the underlying disease. Prophylactically, we prescribed 0.4-1.0 mg/day LMWH (Clexane) for a period of up to 30 days in patients with mild to moderate forms of COVID-19 (regardless of whether the woman remains pregnant or has given birth). After 30 days, patients with continued pregnancy switched to dipyridamole (75 mg x 1-3 times a day). Dipyridamole, as an antiplatelet agent and vasodilator, has a beneficial effect as a drug that reduces the risk of thrombosis, but at the same time does not increase the risk of bleeding in pregnant women about to give birth. In patients who suffered a severe form of the disease, LMWH therapy continued throughout the entire postpartum period (42 days), after which they switched to oral anticoagulants under the control of the above parameters.

5.2. Clinical course of pregnancy, changes in laboratory parameters in women

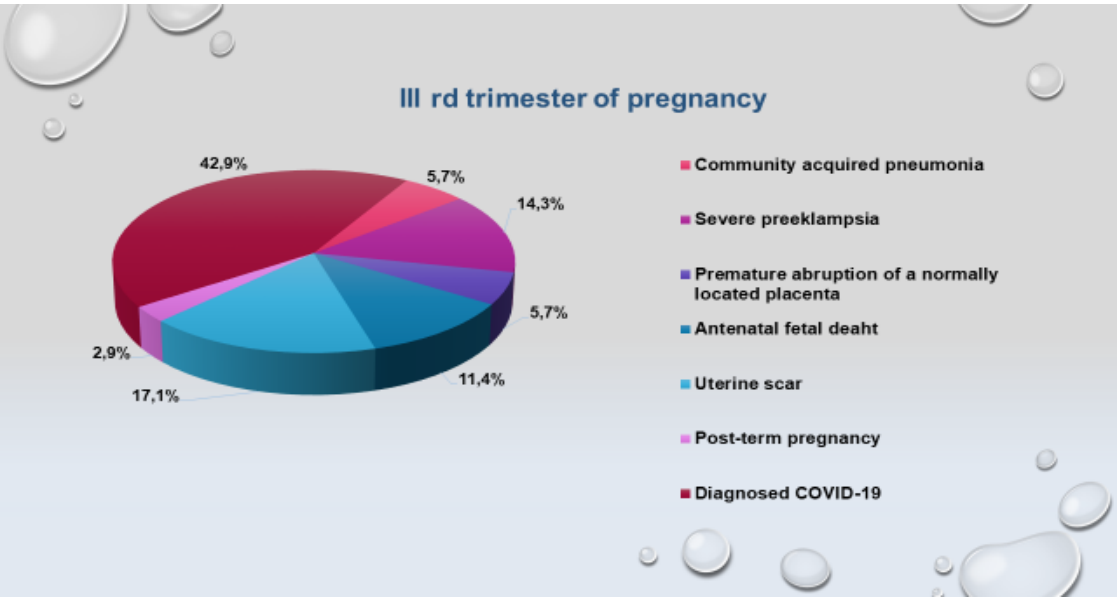
Pictures 5.3–5.5 summarize pregnancy complications in the examined women by trimester.



Picture 5.3. *Complications of the first trimester in pregnant women with Covid-19*



Picture 5.4. *Complications of the second trimester in pregnant women with Covid-19*



Picture 5.5. *Complications of the third trimester in pregnant women with Covid-19*

Thus, the viral infection occurred with complications of the gestational process in all trimesters. We next attempted to make a correlation between disease severity and complication rates.

From the analysis of the course of pregnancy against the background of Covid-19, in different trimesters of pregnancy, and the results obtained on pregnancy outcomes, pregnancy remained in 58 (55.2%) patients, of which 16 women (45.7%) in group Ia, 21 patients in group Ib (60%), and 21 patients in group I (60%).

At the second stage of the study, all these patients who managed to maintain pregnancy were subjected to additional studies at 30, 34, 38 weeks of pregnancy under dynamic observation.

Table 5.1 shows the main parameters of the hemostatic system in 37 pregnant women at 30 weeks (subgroup Ia and Ib with continued pregnancy).

Table 5.1

Changes in laboratory parameters at 30 weeks of pregnancy, (M±m)

Indicators	1a (n=16)	1b (n=21)	P
Clotting time	7,1±0,3	5,9±0,5	<0,05
INR	9,0±0,1	1,6±0,4	<0,001
Fibrinogen	3,9±0,2	5,37±0,01	<0,001
APTT	24,2±0,9	19,1±0,9	<0,001

Platelets	240,5±6,6	215,0±5,6	<0,01
Platelet aggregation	54,2±1,8	49,2±1,7	<0,05
D-dimer	585,5±15,2	785,25±12,6	<0,001
Prothrombin time	11,6±0,6	7,8±0,5	<0,001

Note: *P – reliability of differences between the compared indicators and the indicators during illness.*

The table shows that pregnant women who have had a coronavirus infection in the first trimester of pregnancy remain at risk of increased thrombus formation, which requires appropriate correction; in the second subgroup, a significant increase in aPTT represents a risk of bleeding during childbirth or after childbirth and indicates a low coagulation potential of the blood.

To diagnose the function of the uteroplacental blood flow, at 30 weeks of pregnancy, we performed Doppler measurements in the same patients.

Table 5.2

Research results mother-placenta-fetus system at 30 weeks of pregnancy in pregnant women who have previously had Covid-19

Form of disease/indicators		1a (n=16)	1b (n=21)	R
Umbilical artery	SDR	3,89±0,20	4,53±0.22	<0,05
	ReI	0,82±0,03	0,98±0,02	<0,001
	RiI	1,57±0,05	1,89±0,06	<0,001
Terminal branches of the umbilical artery	SDR	2,7±0,1	3,1±0,1	<0,01
	ReI	0,61±0,02	0,80±0,03	<0,001
	RiI	1,34±0,03	1,56±0,03	<0,001
Middle cerebral artery	SDR	4,87±0,12	5,38±0,18	<0,02
	ReI	0,97±0,03	1,20±0,04	<0,001
	RiI	1,56±0,04	1,79±0,06	<0,001
Aorta	SDR	6,18±0,22	6,26±0,28	>0,5
	ReI	1,1±0,1	1,1±0,1	>0,5
	RiI	1,94±0,07	2,0±0,12	>0,5

Note: *P – reliability of differences between the compared indicators and the indicators during illness.*

As can be seen from this table, all patients still have disturbances in uteroplacental, fetal-placental and intraplacental blood flow. Hemodynamic disturbances of the mother-placenta-fetus system are most pronounced in pregnant women who have had Covid-19 in the second trimester of pregnancy, this is evident from the indicators of umbilical cord artery ReI (0.98±0.02 p <0.001), SDR TBUA (3.1±0.1 p<0.02), as well as aortic RiI (2.0±0.12 p>0.5). Changes in the mother-placenta-fetus system are observed in both the fetal and uteroplacental bloodstreams.

We also assessed the condition and function of the endothelium after suffering from Covid-19 in I and II trimesters of pregnancy at 30 weeks of pregnancy before prescribing corrective therapy (Table 5.3).

Table 5.3

Results of the study of vascular endothelium (V 30 weeks), in pregnant women after a coronavirus infection, (M±m)

Indicators	1a (n=16)	1b (n=21)	R
ET-1, fmol/ml,	0,84±0,04	0,63±0,03	**<0,001**

Note: *P – reliability of differences between the compared indicators and the indicators during illness*

Vascular endothelial dysfunction is an important link in the pathogenesis of complications of pregnancy, childbirth and the postpartum period in women who have suffered coronavirus infection, occupying a leading position in the structure of maternal morbidity and mortality, perinatal mortality and intrauterine growth retardation and fetal pathology [18]. In order to improve endothelial function, we recommended the drug Tivortin 100.0 i/v drip once a day, 7 days, followed by taking the drinking form of the drug for 15 days. One of the main targets of Tivortin is the endothelium, improvement of the function of which entails a wide range of different clinical effects: antihypoxic, membrane stabilizing, cytoprotective, antioxidant, antiradical, detoxification activity, manifests itself as an active regulator of intermediate metabolism in energy supply processes [19]. In addition, Tivortin suppresses the synthesis of endothelin-1, which is a vasoconstrictor and stimulator of proliferation and migration of smooth myocytes of the vascular wall.

To assess the effectiveness and correction of the therapy, hemostasis indicators were assessed at 34 weeks and 38 weeks of pregnancy (Table 5.4).

An important characteristic of the restoration and normalization of hemostasis in pregnant women with Covid-19 and the risk of thrombotic complications by the 34th week of gestation was the concentration of D-dimer, which in all subgroups examined significantly decreased within the first 14 days after the start of therapy, but did not reach normal values.

Table 5.4

Changes in laboratory values at 34 weeks, in pregnant women after a coronavirus infection during therapy, (M±m)

Indicators	1a (n=16)	1b (n=21)	1c (n=21)	P1	P2
Clotting time	7,1±0,3	5,9±0,5	5,4±0,1	<0,05	<0,001
INR	1,0±0,1	1,6±0,4	2,0±0,1	<0,001	<0,001
Fibrinogen	3,9±0,2	5,37±0,01	6,9±0,2	<0,001	<0,001
APTT	24,2±0,9	19,1±0,9	24,1±0,5	<0,001	>0,5
Platelets	240,5±6,6	215,0±5,6	328,2±17,4	<0,01	<0,001
Platelet aggregation	54,2±1,8	49,2±1,7	37,3±1,2	<0,05	<0,001
D-dimer	585,5±15,2	785,25±12,6	1165,5±14,6	<0,001	<0,001
Prothrombin time	11,6±0,6	7,8±0,5	6,9±0,2	<0,001	<0,001

Note: *P1, P2 – reliability of differences in the compared indicators of patients of group 1a with 1b and 1c, respectively*

Table 5.5

Research results mother-placenta-fetus system (in 34 weeks), in pregnant women after a coronavirus infection, (M±m)

Form of disease/indicators		1a (n=16)	1b (n=21)	1c (n=21)	P_1	P_2
Umbilical artery	SDR	4,21±0,12	4,68±0.22	2,32±0,11	>0,1	<0,001
	ReI	0,92±0,03	1,02±0,02	0,56±0,03	<0,01	<0,001
	RiI	1,67±0,04	1,99±0,06	1,15±0,07	<0,001	<0,001
Terminal branches of the umbilical artery	SDR	2,8±0,1	3,2±0,1	3,9±0,2	<0,01	<0,001
	ReI	0,72±0,02	0,88±0,03	0,6±0,03	<0,001	<0,001
	RiI	1,47±0,03	1,65±0,03	0,92±0,04	<0,001	<0,001
Middle cerebral artery	SDR	5,07±0,12	5,68±0,18	3,54±0,12	<0,01	<0,001
	King	1,07±0,03	1,32±0,04	0,69±0,04	<0,001	<0,001
	ReI	1,64±0,04	1,93±0,06	1,02±0,05	<0,001	<0,001
Aorta	RiI	6,32±0,21	6,86±0,22	7,89±0,35	>0,1	<0,001

	ReI	1,2±0,1	1,2±0,1	0,7±0,1	>0,5	<0,001
	RiI	2,04±0,07	2,2±0,12	2,41±0,14	>0,2	<0,02

Note: *P1, P2 – reliability of differences in the compared indicators of patients of group 1a with 1b and 1c, respectively*

Dynamic improvement was also observed in the mother-placenta-fetus system, which was manifested by an improvement in hemodynamic Doppler parameters (Table 5.5).

As can be seen from the results of Doppler measurements given in the table, against the background of the therapy, after 4 weeks we observed an improvement in uteroplacental blood flow, the indicator normalizedel SDR in the umbilical cord arteries from 0.8±0.6 to 2.32±0.11 (p>0.1), ReI TBUA indicators also improved from 0.56±0.04 to 0.72±0.09 (p>0.01).

Table 5.6

Results of the study of vascular endothelium (at 34 weeks) pregnancy in pregnant women with previous coronavirus infection, (M±m)

Indicators	1a (n=16)	1b (n=21)	1c (n=21)	P_1	P_2
ET-1, fmol/ml,	0,94±0,05	0,69±0,04	0,54±0,02	<0,001	<0,001

Note: *P1, P2 – reliability of differences in the compared indicators of patients of group 1a with 1b and 1c, respectively*

Table 5.7

Changes in the parameters of the hemostatic system after a previous coronavirus infection at 38 weeks of pregnancy, (M±m)

Indicators	1a (n=4)	1b (n=20)	1c (n=11)	P1	P2
Clotting time	6,7±0,3	5,4±0,3	5,0±0,1	<0,01	<0,001
INR	1,3±0,1	1,7±0,1	2,0±0,1	<0,01	<0,001
Fibrinogen	4,3±0,2	5,4±0,2	7,1±0,2	<0,001	<0,001
APTT	25,1±1,1	19,7±0,8	23,2±0,8	<0,001	>0,2
Platelets	250,7±6,0	227,0±5,3	314,2±9,3	<0,01	<0,001
Platelet aggregation	53,0±1,4	51,1±1,5	41,4±1,7	>0,5	<0,001
D-dimer	485,0±12,4	624,3±17,2	921,3±14,0	<0,001	<0,001
Prothrombin time	11,9±0,9	8,1±0,7	7,1±0,3	<0,001	<0,001

Note: *P1, P2 – reliability of differences in the compared indicators of patients of group 1a with 1b and 1c, respectively*

Analysis of the results of a study of the hemostasis system of pregnant women showed that under the influence of Clexane, the indicator characterizing the total activity of blood coagulation factors (APTT) normalized by 38 weeks of pregnancy.

Table 5.8

Results of the study of vascular endothelium in pregnant women after a previous coronavirus infection at 38 weeks, (M±m)

Indicators	1a (n=4)	1b (n=20)	1c (n=11)	P_1	P_2
ET-1, fmol/ml,	1,05±0,06	0,78±0,03	0,57±0,03	<0,001	<0,001

Note: *P1, P2 – reliability of differences in the compared indicators of patients of group 1a with 1b and 1c, respectively*

Table 5.9

Research results mother-placenta-fetus system at 38 weeks of pregnancy, (M±m)

Form of disease/indicators		1a (n=4)	1b (n=20)	1c (n=11)	P_1	P_2
Umbilical artery	SDR	4,32±0,17	4,88±0,27	2,47±0,14	>0,1	<0,001
	ReI	1,21±0,03	1,03±0,03	0,67±0,04	<0,001	<0,001
	RiI	1,72±0,07	2,09±0,08	1,25±0,04	<0,001	<0,001
Terminal branches of the umbilical artery	SDR	2,9±0,2	3,3±0,2	4,3±0,3	>0,2	<0,001
	ReI	0,75±0,03	0,92±0,04	0,64±0,03	<0,001	<0,01
	RiI	1,58±0,04	1,72±0,04	1,02±0,06	<0,02	<0,001
Middle cerebral artery	SDR	5,27±0,22	5,94±0,17	3,74±0,28	<0,02	<0,001
	ReI	1,07±0,03	1,37±0,05	0,78±0,05	<0,001	<0,001
	RiI	1,75±0,05	2,03±0,06	1,21±0,05	<0,001	<0,001
Aorta	SDR	6,42±0,21	6,95±0,20	8,04±0,34	>0,1	<0,001
	ReI	1,3±0,1	1,4±0,1	0,9±0,1	>0,5	<0,01
	RiI	2,08±0,09	2,21±0,14	2,45±0,15	>0,5	<0,05

Note: *P1, P2 – reliability of differences in the compared indicators of patients of group 1a with 1b and 1c, respectively*

A comprehensive analysis showed that after 8 weeks, against the background of the therapy, Doppler measurements in pregnant women who had coronavirus infection in the three trimesters of gestation improved: blood circulation parameters in the uterine and spiral arteries, in the umbilical artery and its terminal branches. We also observed a dynamic improvement in blood flow in the spiral arteries, which was recorded in the form of physiological curves of blood flow rates in the uterine

arteries. Improvement in uteroplacental blood flow was observed by normalization of the indicator ReI in the umbilical cord arteries also improved from 0.6±0.8 to 0.4±0.5 ($p>0.02$); ReI in the uterine arteries also improved from 0.35±0.7 to 0.54±0.9 ($p>0.05$).

To prevent the development of circulatory disorders in the mother-placenta-fetus system and treat them when they appear, the main methods are to improve uteroplacental circulation and microcirculation, normalize gas exchange in the mother-placenta-fetus system, improve the metabolic function of the placenta, and restore cellular metabolism disorders. Thus, adequate and timely complex therapy (dipyridamole, L-arginine, clexane) for pregnant women who have had a coronavirus infection, probably can prevent disorders in the mother-placenta-fetus system, helping to increase the likelihood of a favorable pregnancy outcome, which avoids the progression of disorders in the mother-placenta-fetus system.

5.3. Outcomes of pregnancy and childbirth in women with respiratory viral infection

Overall, the majority of pregnancies resulted in term delivery (62 (59%) and vaginal delivery in 39 (45.3%). Premature birth due to obstetric complications and the severity of the mother's condition occurred in 24 (22.9%) women. According to the WHO definition of preterm birth before 37 weeks of gestation and an estimated preterm birth rate of 10% (WHO, 2018), rates of preterm birth in pregnant women. In our study, preterm birth occurred 2.4 times more often among those affected by Covid-19. In this regard, each pregnant patient should be individualized, taking into account the obstetric situation and the state of the mother-placenta-fetus system.

In every fifth (24.4%) patient, the amniotic fluid contained an admixture of meconium. Progressive fetal hypoxia (unsatisfactory/inconclusive fetal condition) was noted in 13 (15%) cases. Delivery by cesarean section occurred in 47 (54.7%)

women according to obstetric indications: acute and progressive fetal hypoxia (unsatisfactory/inconclusive fetal condition) - 13 (27.7%) cases, labor anomalies and uterine scar - 13 (27.7%), PANLP - 4 (8.5%), breech presentation of the fetus - 3 (6.4%). Indications for CS due to the severe condition of the mother were performed in 14 (29%) women.

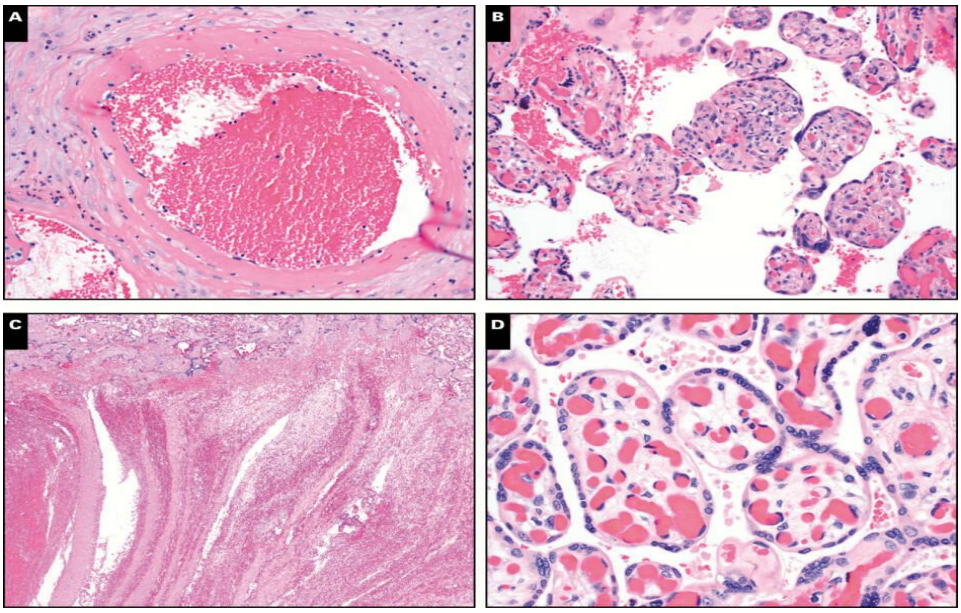
The average blood loss during conservative delivery was 320±29.3 ml, and during cesarean section – 846.6±96.7 ml.

Analysis of the course of labor in three groups showed the following. In patients who suffered a coronavirus infection in the first trimester of pregnancy, birth occurred at an earlier stage of pregnancy, on average at 34.4 ± 3.11 weeks. In patients who had Covid-19 in the second trimester of pregnancy, birth occurred at an average of 35.3 ± 3.9 weeks, with complications occurring in 3 (18.8%) and 13 (37.1%) women. Patients who suffered a coronavirus infection in the third trimester of pregnancy were delivered later in pregnancy, on average at 36.2±4.8 weeks; complications occurred in 10 (28.6%) women.

In the structure of indications for surgical delivery, the inconclusive condition of the fetus in subgroup 1a was 3 (6.4%), in 1b - 4 (8.5%), 1c - 6 (12.8%) cases.

The average weight of newborns at birth was 2500.0±300.0 in subgroup 1a; in subgroup 1b 2800.0±250.0; in subgroup 1 - 2950.0±330.0.

The assessment of the condition of newborns on the Apgar scale was on average 3-4 points in 26 (30.2%) newborns, 5-6 points in 23 (26.7%) newborns, and the remaining 37 (43%) newborns were born in satisfactory condition and assessed on the Apgar scale was 7-8 points and above.



Picture 5.6*. Morphofunctional changes in the placenta of patient I., 28 years old. Diagnosis: Pregnancy II, childbirth II. Urgent birth (suffered coronavirus infection at 10 weeks, mild form) – a) infiltration of plasma cells; b) infiltration of intervillous space by neutrophils; c) an increase in the number of capillaries in the terminal villi; d) lymphocytic focal lesion of the villi (hematoxylin and eosin, x20)*

Characteristics of morphofunctional changes in the placenta in women after Covid-19. We examined the placental tissue of 46 women in labor after suffering from Covid-19 during pregnancy. Despite the serious damage to the placenta that we discovered during histological analysis, the majority of children were able to be born healthy and full-term, with good Apgar scores. However, the results show that much of the blood flow was blocked and many placentas were smaller than they should have been at the appropriate gestational age (Picture 5.6). The average size of the placenta was reduced by 0.7 times at labor of 37 weeks or more, in 48.3% of placentas there were blocked areas of blood flow.

CONCLUSION ON CHAPTER V

Analysis of the study results shows that in patients with viral infections, the incidence of premature birth and the need for surgical delivery is higher than in the population. At the same time, timely started corrective therapy aimed at improving

the function of the uteroplacental circulation allows prolongation of pregnancy and improves perinatal outcomes.

Based on the study, an algorithm for managing pregnancy and childbirth in women who have had Covid-19/seasonal viral infections in different trimesters of pregnancy, depending on the duration and severity of the disease (Application 2).

CONCLUSION

Given that Covid-19 is a viral respiratory infection that has caused an ongoing pandemic, it is important to understand the impact of Covid-19 on mothers and their newborns. Moreover, two other known human coronaviruses (SARS-CoV and MERS-CoV) are associated with adverse clinical outcomes, including life-threatening maternal illness, maternal mortality (in a small but significant number of cases), intrauterine growth restriction, preterm birth, intensive care unit admission of women and newborns, spontaneous abortion, and perinatal death [15, 16].

Pregnant women are more susceptible to developing severe illness following a respiratory viral infection [69]. During the 2009 pandemic outbreak of influenza A virus subtype H1N1 in 2009, pregnant women accounted for only 1% of infected patients but accounted for 5% of all H1N1-related deaths [67].

Our studies have shown that respiratory viral infections in pregnant women lead to significant activation of the hemostatic system (in contrast to the physiological changes in this system that occur). The degree of activation depends on the severity of the viral disease, the addition of obstetric pathology (preeclampsia, PANLP, premature birth, UP, etc.), and the presence of concomitant somatic pathology. Coronavirus infection leads to the intravascular formation of increased concentrations of soluble and insoluble fibrin, a decrease in the number of platelets with an increase in their aggregation function, i.e. conditions are created for increased thrombus formation, which is clinically manifested by the development of severe pneumonia (5-4.8%), respiratory failure (3-2.9%), cardiovascular failure (1-0.95%) in pregnant women. It should be noted that complications of Covid-19 that vary in clinical course (bleeding after childbirth or thrombosis of the vascular bed) cause an almost identical intensification of thrombus formation. This once again confirms the nonspecificity of hemostasis disorders in Covid-19 under the influence of various causal causes. Noteworthy is the fact that the somatic pathology that some pregnant women had had a less activating effect on hemostasis on the patients'

condition than the coronavirus infection itself. Disturbances in the hemostatic system lead not only to clinically significant thromboembolic complications, but also play a leading role in the pathogenesis of Covid-19 and its complications [26].

Timely diagnosis of thrombophilia and other hemostasis disorders in pregnant women with respiratory viral infections is not only an effective method for diagnosing the severity of the disease, which allows for competent specific and nonspecific prevention of thrombotic complications of the new coronavirus infection, but also helps prevent obstetric hemorrhage during childbirth. This approach significantly improves perinatal outcomes in pregnant women. To improve perinatal outcomes and the risks of additional pregnancy complications in women with respiratory viral infections, it is also necessary to prescribe drugs to improve blood flow in the mother-placenta-fetus system. Changes in this system are proven by Doppler studies of blood flow.

Our study is a definite step in the further study of the problem of viral infections and their complications in obstetrics. New information about the impact of respiratory viral infections on the mother-placenta-fetus system will help preserve the health of future generations during the development of seasonal respiratory viral infections.

REFERENCES

1. Abdullaeva L.M., Kim V.S. Perinatal outcomes in patients with COVID-19 // Journal of Theoretical and Clinical Medicine. – 2021 – T. 1. - No. 6. – pp. 12-14.
2. Abdurakhimov A. Kh., Khegai L. N., Yusupova Sh. K. COVID-19 and its complications //Re-health journal. – 2021. – No. 4 (12). – P. 61-74.
3. Alimova H.A. The art of maintaining health in the context of the COVID-19 pandemic // XI International Avicenna Readings, scientific and practical conference - Abu Ali Ibn Sino (Avicenna) and COVID - 19. - 2021. - pp. 11-13.
4. Ashurova D.A., Mirzaabdullaeva D.I., Muminov S.O. Approaches to delivery of pregnant women who have had COVID-19 // Journal of Theoretical and Clinical Medicine. – 2021. – T. 1. - No. 6. – pp. 31-34.
5. Vorobyov A. I. et al. Hypercoagulable syndrome: classification, pathogenesis, diagnosis, therapy // Hematology and Transfusion. - 2016. - T. 61. – No. 3. – P. 116-122.
6. Temporary guidelines “Prevention, diagnosis and treatment of new coronavirus infection (COVID-19)” // Version 9. – (10/26/2020). – pp. 235-238.
7. Temporary recommendations for the management of patients infected with coronavirus infection COVID-19 //Ministry of Health of the Republic of Uzbekistan. – Version 8. – 2021. – pp. 19-28.
8. Dzhumaev K.Ch., Eshimbetova G.Z. Experience of pregnancy management in women with COVID-19 // Journal of Theoretical and Clinical Medicine. – 2021. – T. 1. – No. 6. – P. 51-53.
9. Dzhumaev K.Ch., Eshimbetova G.Z., Musakhodzhaeva D.A., Dranenko L.M., Shaikramova N.H. Features of the course of pregnancy, childbirth and the postpartum period in women with a confirmed diagnosis of COVID-19 //Tibbiyotda Yangi Kun. – 2021. – 3 (35/1). – pp. 110-113.

10. Dustova N.K., Ikhtiyarova G.A. Infection of the placenta in pregnant women who have had coronavirus infection during the pandemic // Journal of Theoretical and Clinical Medicine. – 2021. – T. 1. – No. 6. – P. 56-59.

11. Dustova N.K., Ikhtiyarova G.A. Prediction of fetoplacental insufficiency in pregnant women who have had coronavirus infection //Tibbiyotda Yangi Kun. – 2021. – 3 (35/1). – pp. 380-384.

12. Dremina N.N., Shurygin M.G., Shurygina I.A. Endothelins in health and pathology // International Journal of Applied and Fundamental Research. – 2016. – No. 10-2. pp. 210-214

13. Instructions, INN: Arginine, manufacturer: Yuria-Pharm LLC, anatomical-therapeutic-chemical classification, registration number in the Republic of Kazakhstan: No. RK-LS-5№019778, Republic of Kazakhstan: 05/04/2018 - 05/04/2023. pp. 27-29.

14. Karimova L.A., Nadyrkhanova N.S., Pakhomova Zh.E., Garib F.Yu., Levitskaya Yu.V., Mirzaabdullaeva D.I. and others. SARS-COV-2 virus neutralizing activity of umbilical cord blood // Journal of Theoretical and Clinical Medicine. – 2021. – T. 1. – No. 6. P. 86-89.

15. Komilova M. S., Pakhomova Zh. E. The importance of the endothelium in the development of complications of the gestational period // Russian Bulletin of Obstetrician Gynecologist. – 2015. – No. 1 (15). WITH. 18-23.

16. Lutsay E. D. et al. On the issue of the morphology of the human placenta // Orenburg Medical Bulletin. – 2021. – T. 9. – No. 1 (33). – pp. 10-17.

17. Makatsaria A.D. Intravascular coagulation in Covid-19 determines the entire course of the disease, interview dated 5/5/2020.

18. Malinnikova E. Yu. New coronavirus infection. Today's view of the 21st century pandemic // Infectious diseases: News. Opinions. Education. – 2020. – T. 9. – No. 2 (33). – P. 18-32.

19. Makhkamova I.M. Complications after COVID-19. Condition in pregnant women //XI International Avicenna Readings, scientific and practical conference - Abu Ali Ibn Sino (Avicenna) and COVID - 19. - 2021. - pp. 26-27.

20. Momot A.P. et al. Modern methods for recognizing the state of thrombotic readiness. – 2011.

21. Nadyrkhanova N.S., Karimova L.A., Akhmadiev E. Course analysis of coronavirus infection SaRS-COV-2 (COVID -19) in pregnant women //Tibbiyotda Yangi Kun. – 2021. – 3 (35/1). – S. 182-185.

22. Nazhmutdinova D.K., Khikmatullaeva M.R. Perinatal outcome in pregnant women who have had COVID-19 // Journal of Theoretical and Clinical Medicine. – 2021. – T. 1. – No. 6. – P.115-118.

23. Vorobyov P. A., Elykomov V. A. Recommendations for the diagnosis and intensive therapy of disseminated intravascular coagulation syndrome in viral lung disease // Problems of standardization in healthcare. – 2020. – No. 5-6. – P. 71-94.

24. Roitman E.V., Bulanov A.Yu., Pechennikov V.M. Dosing of low molecular weight heparins and anti-factor Xa activity in patients with the new coronavirus infection COVID-19 // Thrombosis, hemostasis and rheology. – 2020. – No. 4. – pp. 57-67.

25. Sadikova D.R., Sharipova M.Sh. Causes of serious complications (thrombosis) during pregnancy in women who had COVID-19 in the second trimester of pregnancy - 2021. - C. 34-36.

26. Turbanova U.V., Kayumova D.T., Nazarova D.E., Parvizi N.I. Yangibaeva D.T. Features of the course of pregnancy and its outcome in women who had COVID-19 during pregnancy (2 clinical cases) // Journal of Theoretical and Clinical Medicine. – 2021. – T. 1. - No. 6. pp. 152-156.

27. Khodzhaeva A.S. COVID-19 and women's health // Journal of Theoretical and Clinical Medicine. – 2021. – T. 2. – No. 6. – P. 167-169.

28. Shopulotova Z.A., Khudoyarova D.R., Shopulotov Sh.A. Coronavirus infection and motherhood //XI International Avicenna Readings, scientific and practical conference - Abu Ali Ibn Sino (Avicenna) and COVID-19. – 2021. – pp. 46-47.

29. Shatokhin Yu. V., Snezhko I. V., Ryabikina E. V. Impaired hemostasis during coronavirus infection // South Russian Journal of Therapeutic Practice. – 2021. – T. 2. – No. 2. – pp. 6-15.

30. Ahmed S., Zimba O., Gasparyan A. Y. Thrombosis in Coronavirus disease 2019 (COVID-19) through the prism of Virchow's triad //Clinical Rheumatology. – 2020. – T. 39. – C. 2529-2543.

31. Alfaraj S. H., Al-Tawfiq J. A., Memish Z. A. Middle East Respiratory Syndrome Coronavirus (MERS-CoV) infection during pregnancy: Report of two cases & review of the literature. – 2019. C. - 501–503.

32. Alzamora M. C. et al. Severe COVID-19 during pregnancy and possible vertical transmission //American journal of perinatology. – 2020. – T. 37. – №. 08. – C. 861-865.

33. Kilpatrick S. K. et al. Severe maternal morbidity: screening and review //American journal of obstetrics and gynecology. – 2016. – T. 215. – №. 3. – C. B17-B22.

34. Arora N. et al. Microbial vertical transmission during human pregnancy //Cell host & microbe. – 2017. – T. 21. – №. 5. – C. 561-567.

35. Breslin N. et al. COVID-19 infection among asymptomatic and symptomatic pregnant women: two weeks of confirmed presentations to an affiliated pair of New York City hospitals. //American Journal of Obstetrics & Gynecology MFM. – 2020. – T.100-118.

36. Chen Y. H. et al. Pneumonia and pregnancy outcomes: a nationwide population-based study //American journal of obstetrics and gynecology. – 2012. – T. 207. – №. 4. – C. 288-295.

37. Coronavirus disease 2019 (COVID-2019). Situation report 54. Geneva: World Health Or-ganization; 2020. Accessed March 15, 2020.

38. Di Mascio D. et al. Outcome of coronavirus spectrum infections (SARS, MERS, COVID-19) during pregnancy: a systematic review and meta-analysis //American journal of obstetrics & gynecology MFM. – 2020. – Т. 2. – №. 2. – С. 100-107.

39. Favre G. et al. 2019-nCoV epidemic: what about pregnancies? //Lancet (London, England). – 2020. – Т. 395. – №. 10224. – С. 40-53.

40. Fornari F. Vertical transmission of Covid-19-a systematic review //Journal of Pediatrics, Perinatology and Child Health. – 2020. – Т. 4. – №. 2. – С. 7-13.

41. Hippensteel J. A., Burnham E. L., Jolley S. E. Prevalence of venous thromboembolism in critically ill patients with COVID-19 //British Journal of Haematology. – 2020. – Т. 190. – №. 3. – С. 134-145.

42. Huang C. et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China //The lancet. – 2020. – Т. 395. – №. 10223. – С. 497-506.

43. Iba T. et al. New criteria for sepsis-induced coagulopathy (SIC) following the revised sepsis definition: a retrospective analysis of a nationwide survey. BMJ Open. 2017; 7 (9): e017046. PMID: 28963294 //Thromb Haemost. – 2017. – Т. 117. – №. 3. – С. 437-444.

44. Iqbal S. N. et al. An uncomplicated delivery in a patient with Covid-19 in the United States //New England Journal of Medicine. – 2020. – Т. 382. – №. 16. – С. 34-36.

45. Jeong S. Y. et al. MERS-CoV infection in a pregnant woman in Korea //Journal of Korean medical science. – 2017. – Т. 32. – №. 10. – С. 1717-1720.

46. Khan S. et al. Association of COVID-19 with pregnancy outcomes in health-care workers and general women //Clinical microbiology and infection. – 2020. – Т. 26. – №. 6. – С. 788-790.

47. Knight M. et al. Characteristics and outcomes of pregnant women admitted to hospital with confirmed SARS-CoV-2 infection in UK: national population based cohort study //bmj. – 2020. – T. 369-376.

48. Lam C. M. et al. A case-controlled study comparing clinical course and outcomes of pregnant and non-pregnant women with severe acute respiratory syndrome //BJOG: An International Journal of Obstetrics & Gynaecology. – 2004. – T. 111. – №. 8. – C. 771-774.

49. Lapinsky S. E. Acute respiratory failure in pregnancy //Obstetric medicine. – 2015. – T. 8. – №. 3. – C. 126-132.

50. Li Y. et al. Lack of vertical transmission of severe acute respiratory syndrome coronavirus 2, China //Emerging infectious diseases. – 2020. – T. 26. – №. 6. – C. 1335-1339.

51. Liu D. et al. Pregnancy and Perinatal Outcomes of Women With Coronavirus Disease (GOV ID-19) Pneumonia: A Preliminary Analysis (vol 96, pg 563, 2020) //AMERICAN JOURNAL OF ROENTGENOLOGY. – 2020. – T. 215. – №. 1. – C. 262-265.

52. Liu Y. et al. Clinical manifestations and outcome of SARS-CoV-2 infection during pregnancy //J infect. – 2020. – T. 10. – C. 458-471.

53. Magee LA. UKOSS in context [electronic response to Knight M. et al. Characteristics and outcomes of pregnant women admitted to hospital with confirmed SARS-CoV-2 infection in UK: national population based cohort study //bmj. – 2020. – T. 369-376.

54. Malik A. et al. Middle east respiratory syndrome coronavirus during pregnancy, Abu Dhabi, United Arab Emirates, 2013 //Emerging infectious diseases. – 2016. – T. 22. – №. 3. – C. 515.

55. Moola S. et al. Chapter 7: Systematic reviews of etiology and risk //Joanna briggs institute reviewer's manual. The Joanna Briggs Institute. – 2017. – T. 5.

56. Mor G., Cardenas I. The immune system in pregnancy: a unique complexity //American journal of reproductive immunology. – 2010. – Т. 63. – №. 6. – С. 425-433.

57. Patanè L. et al. Vertical transmission of coronavirus disease 2019: severe acute respiratory syndrome coronavirus 2 RNA on the fetal side of the placenta in pregnancies with coronavirus disease 2019–positive mothers and neonates at birth //American journal of obstetrics & gynecology MFM. – 2020. – Т. 2. – №. 3. – С. 100-145.

58. Penfield C. A. et al. Detection of SARS-COV-2 in Placental and Fetal Membrane Samples [published online ahead of print, 2020 May 8] //Am J Obstet Gynecol MFM. – 2020. – Т.100-133.

59. Royal College of Obstetricians and Gynecologists. Coronavirus (COVID-19) infection in pregnancy—information for healthcare professionals. March 2020. Availabel at: https:// www.rcog.org.uk/globalassets/documents/ guidelines/coronavirus-covid-19-infection-in- pregnancy-v2-20-03-13.pdf

60. Schwartz D. A., Graham A. L. Potential maternal and infant outcomes from coronavirus 2019-nCoV (SARS-CoV-2) infecting pregnant women: lessons from SARS, MERS, and other human coronavirus infections //Viruses. – 2020. – Т. 12. – №. 2. – С

61. Sisman J. et al. Intrauterine transmission of SARS-COV-2 infection in a preterm infant //The Pediatric infectious disease journal. – 2020. – Т. 39. – №. 9. – С. e265-e267.

62. Startseva T. V. et al. Pregnancy and Zika virus //Obstetrics, Gynecology and Reproduction. – 2020. – Т. 14. – №. 2. – С. 229-238.

63. Stockman L. J. et al. SARS during pregnancy, United States. Emerg Infect Dis – 2004. – С.1689–1690.

64. Stroup D. F. et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting //Jama. – 2000. – Т. 283. – №. 15. – С. 2008-2012.

65. Sutton D. et al. Universal screening for SARS-CoV-2 in women admitted for delivery //New England Journal of Medicine. – 2020. С. 316-322.

66. Tang N. et al. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia //Journal of thrombosis and haemostasis. – 2020. – Т. 18. – №. 4. – С. 844-847.

67. Wang X. et al. A case of 2019 Novel Coronavirus in a pregnant woman with preterm delivery //Clinical infectious diseases. – 2020. – С. 200-204.

68. World Health Organization. Guidelines for the global surveillance of severe acute respiratory syndrome (SARS). Geneva: World Health Or-ganization; 2004. Accessed March 15, 2020;

69. Xiong X. et al. Vaginal delivery report of a healthy neonate born to a convalescent mother with COVID-19 //Journal of medical virology. – 2020. – Т. 92. – №. 9. – С. 1657-1659.

70. Yates L. et al. Influenza A/H1N1v in pregnancy: an investigation of the characteristics and management of affected women and the relationship to pregnancy outcomes for mother and infant //Health technology assessment. – 2010. – Т. 14. – №. 34 Article 2. – С. 109-182.

Application 1

Scale for assessing the risk of developing undeveloped pregnancy in COVID-19

№	Indicators	Main Features	Points
1	Age	Age from 18 to 34 years	0
		Age over 35 years	1
		Age up to 18 years	2
2	Course of COVID-19	lung	0
		moderate severity	1
		heavy	2
3	Somatic pathology	No	0
		Gastrointestinal diseases	1
		Cardiovascular diseases, diabetes	2
		Chronic foci of infection	3
4	BMI	18-24	0
		25-30	1
		30 or more	2
5	History of spontaneous abortions (including non-developing pregnancy)	1	1
		2	2
		2 or more	3
6	History of induced abortions	No	0
		1-2	1
		2 or more	2
7	History of preeclampsia/eclampsia; PANLP	No	0
		There is	2
8	Total platelet count $1x10^9$ /l	$180\text{-}310 \times 10^9$ /l	0
		$179\text{-}101 \times 10^9$ /l	1
		100×10^9 /l and less	2
9	D-dimer	Within normal limits	0

		Slightly increased	1
		Significantly increased	2
10	Prothrombin time	3-6	0
		>6 sec	2
11	Fibrinogen	2.6-5.6 g/l	0
		2.5-2.1 g/l	1
		2.0 g/l day cam	2
12	ET-1, pgmol/l	0,1-1,0	0
		1,1-2,0	1
		2.1 or more	2
13	CRP, mg/l	Until 10	0
		10-20	1
		More than 20	2
14	Anemia	Hemoglobin >90 g/l	1
		Hemoglobin 71-90 g/l	2
		Hemoglobin < 70 g/l	3

Application 2

ALGORITHM FOR MANAGING PREGNANCY AND CHILDREN IN WOMEN WHO HAVE COVID-19 IN DIFFERENT TRIMESTERS OF PREGNANCY