Scripta Scientifica Medica, 2023;55(1):19-26
DOI: 10.14748/ssm.v55i1.9270

ISSN 0582-3250 (Print)
ISSN 1314-6408 (Online)

ORIGINAL ARTICLES

CLINICAL ANALYSIS OF PREGNANT WOMEN WITH COVID-19 IN BULGARIA

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ABSTRACT

INTRODUCTION: The coronavirus disease 2019 (COVID-19) pandemic remains a global threat. The clinical course of the infection in pregnant women and its impact on their fetuses are currently discussed topics among medical specialists.

AIM: The aim of this article is to evaluate the clinical course of COVID-19 in pregnant women and assess the effects of the disease on their fetuses.

MATERIAL AND METHODS: Ten pregnant women in the third trimester with COVID-19, hospitalised at the labour ward of St. Anna Hospital in Varna were examined between November 2020 and May 2021. A clinical and laboratory study was conducted. The nasopharyngeal swab samples were collected and tested positive using reversed transcriptase-polymerase chain reaction (COVID-19 real-time PCR). Cardiotocography and abdominal ultrasound were used to evaluate the fetuses' condition. Statistic methods were used for data processing.

RESULTS: The clinical presentation of coronavirus infection of the ten hospitalized pregnant women with COVID-19 includes fever, cough, shortness of breath, and fatigue. The laboratory tests revealed absolute lymphopenia, elevated C-reactive protein, and elevated D-dimer. All women showed evidence of hypoxemia, accompanied in 90% of cases by respiratory alkalosis. No signs of preterm birth or presence of fetal distress were established.

CONCLUSION: The clinical course of COVID-19 showed no difference in pregnant women and non-pregnant individuals. However, the physiological adaptation to pregnancy with its clinical and laboratory variations may make assessing the effects of COVID-19 on pregnant women difficult. In mild and moderate cases, COVID-19 does not aggravate the course of pregnancy and does not threaten the fetal condition. Additional systematic studies are needed to evaluate the effects of COVID-19 on pregnant women.

Keywords: *COVID-19, pregnancy, fetus, pneumonia, absolute lymphopenia, hypoxemia*

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Received: February 12, 2023
Accepted: March 23, 2023

INTRODUCTION

Over 770 million people worldwide are estimated to have had coronavirus disease 2019 (COVID-19) by September 2023, resulting in more than 6.96 million deaths (1). The etiology, pathogenesis, and symptoms of the coronavirus infection have been investigated in the period of almost 4 years since the beginning of COVID-19 pandemic; accurate diag-

nostic methods were introduced; vaccines were invented. However, certain unresolved problems and questions still remain to this day. One of these conundrums is the information about the course of the coronavirus disease in pregnant women, which is inconsistent and frequently versatile. Furthermore, there is an absence of a unified approach in terms of prevention and treatment of COVID-19 in this vulnerable group.

Pregnancy is associated with increased severity of some viral infections such as severe acute respiratory syndrome (SARS) and middle east respiratory syndrome (MERS), both caused by coronaviruses. The death rate of affected pregnant women reached 25–30% (2). In addition, there is strong evidence that pregnant women are at higher risk of severe illness and mortality from influenza, varicella, viral hepatitis E, Ebola and Lassa hemorrhagic fevers (3). New studies demonstrate that pregnant women with a symptomatic form of coronavirus disease 2019 are at a higher risk of being admitted to an intensive care unit (ICU) and needing mechanical ventilation. Advanced maternal age, high body mass index (BMI), the presence of chronic diseases, and non-white race are suggested to be risk factors of severe course of COVID-19 in pregnant patients (4).

The pregnancy outcome and the fetal condition in pregnant women with COVID-19 are important issues to be solved. There is limited data about the effects of the coronavirus infection during the first trimester of pregnancy. A case-control study conducted by Cosma et al. did not find an elevated risk of miscarriage among women in the first trimester of pregnancy with COVID-19 compared to healthy controls (5). Sacinti and others found an increased frequency of early miscarriages among these patients during the COVID-19 pandemic (6). Simultaneously the researchers point out that advanced pregnancy in women with COVID-19 results in premature birth more often than in the general population – 12.9% against 10.9% (7). A higher risk of cesarean section, which, according to different sources, varies between 70% and 84.7%, is observed as well (8).

It is known that certain viruses cross the placenta and cause different cognitive disorders (3). Whether severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is capable of this was an object of several studies. The placental cells express ACE2 receptors and serine proteases TMPRSS2, which are necessary for SARS-CoV-2 to accomplish a cellular invasion. Therefore, a vertical viral transmission can occur. Furthermore, a presence of anti-SARS-CoV-2 IgM in the blood of newborns of mothers infected with SARS-CoV-2 has been detected. These high molecular weight antibodies would not be able to cross the placental barrier, which suggests that an infection of the embryo is highly probable (9). Currently, the lack of uniform criteria for testing newborns born to women with COVID-19 does not allow assessment of this risk (8). The reported neonatal results of babies delivered by mothers with confirmed COVID-19 are mostly favourable, perinatal infection has been registered in only 2.6% of the cases, mostly in mothers infected with COVID-19 within 1 week before giving birth (7). These newborns have mild or no symptoms, probably because of a low expression of serine protease TMPRSS2, which does not allow SARS-CoV-2 to enter the target cells and cause a typical clinical presentation of COVID-19 (10).

AIM

To study the clinical course of COVID-19 in pregnant women, we set the following tasks:

1. To analyse the clinical and laboratory changes in pregnant women with COVID-19, examined between November 2020 and May 2021;
2. To define the severity of COVID-19 in the patients;
3. To determine the presence/absence of fetal distress during coronavirus infection.

MATERIALS AND METHODS

During the period November 2020 – May 2021, 10 women with COVID-19 were hospitalised at the labour ward of St. Anna Hospital in Varna. Their disease histories were analysed retrospectively. The diagnosis was made according to the definition of the European Centre for Infectious and Parasitic Diseases for confirmed COVID-19 cases, which includes the detection of antigen or nucleic acid SARS-CoV-19 in a clinical sample (11). The nasopharyngeal swab samples were collected and tested positive using reversed transcriptase-polymerase chain reaction (COVID-19 real-time PCR).

The medical history, clinical manifestations, and laboratory changes have been studied in every patient. The disease severity of COVID-19 was stratified according to the current algorithm of the World Health Organization (WHO) (12) (Table 1).

Table 1. WHO definitions of disease severity for COVID-19 (12).

Critical COVID-19	Defined by the criteria for acute respiratory distress syndrome (ARDS), sepsis, septic shock, or other conditions that would normally require the provision of life-sustaining therapies such as mechanical ventilation (invasive or non-invasive) or vasopressor therapy
Severe COVID-19	Defined by any of: oxygen saturation < 90% on room air; severe pneumonia; signs of severe respiratory distress (in adults, accessory muscle use, inability to complete full sentences, respiratory rate > 30 breaths per minute; and, in children, very severe chest wall in-drawing, grunting, central cyanosis, or presence of any other general danger signs including inability to breastfeed or drink, lethargy, convulsions or reduced level of consciousness).
Non-severe COVID-19	Defined as the absence of any criteria for severe or critical COVID-19

Transabdominal fetal ultrasound and cardiotocography (CTG) were performed to evaluate fetal development and the presence/absence of fetal distress.

RESULTS

Ten women, aged 19 to 43 years, with COVID-19 were treated during the period November 2020 – May 2021. All of them were in the third trimester, between 28 and 37 gestational weeks, with 8 of them having a singleton pregnancy, and 2 – twin pregnancies (Table 2).

Table 2. Sociodemographic and obstetric characteristics of the patients (n = 10).

Age (years)	19–43 (average 31.9 ± 6.7)
Gestational age	28–37 (average 32.8 ± 3)
Number of fetuses	1–8 (80%) 2–2 (20%)

The case history of all patients did not reveal any underlying conditions, except 1 woman with autoimmune thyroiditis. Before the current hospitalisation, the pregnancy in 7 (70%) proceeded without complications, and in 3 (30%) it was accompanied by mild iron deficiency anemia.

Six (60%) women did not report any contact with infectiously ill individuals and denied recent travels abroad. Four (40%) women reported contact with SARS-CoV-2 infected persons. A COVID-19 vaccine was never administered to any of them.

Upon admission to the hospital, all women (100%) had complaints of cough, shortness of breath, and fatigue. One (10%) was afebrile, 3 (30%) were subfebrile, and the body temperature of 6 (60%) was above 38°C. Auscultation of the lungs revealed in abnormal lung sounds 9 (90%) – decreased breath sounds, crackles and wheezes with different localizations. Only in 1 (10%) patient, the auscultation of the lungs did not show deviations from the norm. To clarify the pathological pulmonary findings, the women were offered conventional radiography (CRG) of the chest. In 2 informed consent for conducting the procedure was received, and pneumonia was confirmed in the both cases.

We analysed the laboratory changes in the patients (Table 3). The complete blood count (CBC) indicated neutrophilic leucocytosis in 1 patient, only neutrophilia – in 2 patients, and normal leucocyte count in 7 patients. Absolute lymphopenia was detected in 6 women.

We found that C-reactive protein (CRP≥5 mg/L) was elevated in all patients – 10 (100%), with the average value being 40.87±13.4 mg/L. Glucose, total protein, albumin, and liver enzymes were within the normal limits for the age and sex. The analysis of the coagulation status showed that in all 10 (100%) pregnant women there were elevated D-dimer lev-

Table 3. Laboratory results of the patients.

Component		Patient									
	Reference Values	1	2	3	4	5	6	7	8	9	10
Hemoglobin, g/L	120–180	121	113	112	114	105	122	106	124	116	101
Red Blood Cell Count, $x10^{12}$/L	4.00–5.40	4.25	4.27	3.62	3.68	4.41	3.93	3.93	4.06	3.66	3.98
White Blood Cell Count, $x10^9$/L	3.50–10.50	9.7	4.9	6.8	6.0	10.3	6.1	6.3	6.2	12.9	9.1
Neutrophil, $x10^9$/L	2.00–7.50	8.3	3.6	5.6	5.2	8.1	4.9	5.1	5.3	11.8	7.4
Neutrophil, %	50.00–75.00	85.0	73.4	81.6	86.6	78.4	80.3	78.9	84.5	91	81.1
Lymphocyte, $x10^9$/l	1.50–4.50	1.1	1.0	0.8	0.6	1.7	0.9	0.9	0.7	0.6	1.5
Lymphocyte, %	37.50–45.00	11.5	20.4	12.6	10.0	16.6	14.7	15.1	12.3	5.2	16.1
Platelet Count, $x10^9$/L	140.00–440.00	321	141	224	161	311	198	198	208	215	220
CRP	0.0–5.0	34.9	38.02	35	48	20.91	31.8	64.23	42.44	60.7	32.68
D-dimer	0–275	2449.9	1130	485	945	5631	1120	288	798	1928	2547

els with an average value of 1732.19±1573.71 ng/mL without other deviations in the blood coagulation.

We also analysed the presence of deviations in the acid-base balance (ABB) of the capillary blood upon admission. Fully compensated respiratory alkalosis was observed in 5 (50%), 2 (20%) appeared in the process of partial compensation of respiratory alkalosis, 2 (20%) had uncompensated respiratory alkalosis, 1 (10%) was with fully compensated respiratory acidosis. Furthermore, 10 (100%) women had hypoxemia (pO_2<11.1 kPa) (Table 4).

The gynaecological examination revealed that the cervix in 8 (80%) women was with normal length, without disclosure, the amniotic sac was intact; in 2 (20%) the cervix was sacralised, softened, with disclosure 0.5 cm and preserved amniotic sac.

Cardiotocography was performed to determine fetal well-being. It showed that 6 (43%) of the fetuses had a heart rate (HR) of 140 beats per minute, 4 (29%) had HR of 150 beats per minute, 1 (7%) – 137 beats per minute, and 1 (7%) – 160 beats per minute; all with constant variability and reactivity. During the hospitalisation, an ultrasound of the uterus with an abdominal transducer was performed. It established no evidence of intrauterine retardation.

The treatment of all the patients included empiric broad-spectrum antibiotics, anticoagulants, corticosteroids, tocolytic therapy, antipyretics, and oxygen, when necessary. All of the patients were discharged from the hospital in improved general condition with preserved pregnancy. The follow-up control examinations on the 7th and 15th day since the

Table 4. Changes in ABB.

Component		Patient									
	Reference Values	1	2	3	4	5	6	7	8	9	10
pH	7.350–7.450	7.418	7.405	7.458	7.408	7.439	7.402	7.466	7.568	7.468	7.425
pO2, kPa	11.1–14.4	8.21	8.43	8.97	8.22	10.6	8.41	8.91	7.7	9.69	7.47
pCO2kPa	4.27–6.40	4.10	3.54	3.49	7.21	3.85	3.58	3.72	3.05	3.3	4.14
HCO3, mmol/L	21.8–26.9	21.3	19.0	21.0	31.5	19.1	18.8	22.4	24.7	20.9	19.9
Base excess (BE)	-3–+3	-4.2	-3.5	-4.9	8.6	-4.1	-7.5	-3.3	-1.1	-5.4	-3.7
SO2,%, mmol/L	95–99	92.2	91.5	95.9	91.4	89	92.2	94.7	96.4	96.9	89.9

dehospitalisation did not show any deviations in the patient's conditions nor the course of the pregnancy.

DISCUSSION

We presented a series of clinical cases of COVID-19 in 10 pregnant women in the third trimester, hospitalised in St. Anna Hospital in Varna during the period between November 2020 and May 2021, who were admitted with complaints of fever, cough, shortness of breath, and fatigue. The analysis of the literature indicates that similar symptoms are distinctive for pregnant women with COVID-19 and they do not alter from the complaints of non-pregnant individuals with the same diagnosis (8, 9). Simultaneously, the clinicians have to consider that fever, cough, shortness of breath, and fatigue could be a result of the physiological adaptation of the female body to the pregnancy. They are a consequence of anatomical and functional changes in the cardiorespiratory and immune systems, and are due to the compression of the chest by the growing uterus, suppression of Th1-proinflammatory reactions, decreased amount of circulating plasmacytoid dendritic cells and natural killer cells; an increase in the volume of circulating blood in the woman's body, increase in HR and stroke volume (8, 13). However, WHO observes that pregnant and recently pregnant women with COVID-19 are less likely to be symptomatic or exhibit symptoms such as fever, dyspnea, and myalgia in comparison to non-pregnant women of reproductive age (12), as around 30% pregnant against 10% of non-pregnant women may show the symptoms of the infection (8). Since the hospitalisation of pregnant women in the labour ward does not require COVID-19 testing, the absence of symptoms specific to the disease did not allow us to establish the incidence of asymptomatic infection among this cohort.

The clinical examination of the patients revealed that the majority of the patients (90%) had different respiratory symptoms – shortness of breath and dry and/or wet rales with different lung localization. These findings with the aforementioned complaints make the diagnosis of pneumonia highly suspicious. A differential diagnosis of lung inflammation was considered in only 2 (20%) women, as a result of the refusal of the pregnant women to give the informed consent to conduct an X-ray examination. Pregnancy is not a contraindication for an X-ray examination, especially in the presence of clinical indications for its conduction. During the COVID-19 pandemic era, X-ray examination and computed tomography of the chest are indispensable tools in the diagnostics and control of the treatment of COVID-19 patients. It was established that radiation risk in pregnant women with COVID-19 does not differ from those in non-pregnant individuals with the same diagnosis (14). It has been established that the radiation risk for the embryo depends on its gestational age and the radiation dose (15). This risk, as well as the anxiety of the pregnant woman, could be eliminated by using lung ultrasound, which is capable of proving COVID-19 pneumonia with high precision (above 90% sensitivity and 95% specificity). Additionally, this method is economically beneficial and can be used repeatedly during the treatment (16). Regardless of its advantages, at the moment there is no unified approach and standardized criteria for ultrasound diagnosis of COVID-19 pneumonia.

We indicated that absolute lymphopenia is the most common pathological deviation in CBC (Table 3). According to the Centers for Disease Control and Prevention (CDC), lymphopenia occurs in 83% of hospitalised patients with COVID-19 (17). Moreover, the severity of lymphopenia is directly proportional to the severity of COVID-19 (18). There are different reasons for such decrease in the absolute lymphocyte count: increased level of pro-inflammatory cytokines, leading to escalated apoptosis of lymphocytes; hyperlactatemia, inhibiting lymphopoiesis in the course of severe coronavirus infection; the treatment of COVID-19 with drugs that suppress lymphopoiesis (18). Lymphopenia is also reported in pregnant women with COVID-19 (8). The question is whether the decreased lymphocytes in the blood of pregnant women are caused by the coronavirus infection and whether they can be used as a prognostic factor given that lymphopenia in this patient group is a result of the physiological immunomodulation for implantation and carrying of a semi-allograft fetus (19) would be determined in subsequent studies.

We found elevated CRP and D-dimer levels are a characteristic feature in our patients (Table 3). CPR is the acute phase protein, widely used as a marker for systemic inflammation and severe infections, mostly of bacterial origin. It has been proven that its value rises proportionally with the severity of the CO-

VID-19 infection, in pregnant women as well (17, 20, 21). COVID-19 in our patients was not critical, therefore we observed relatively light elevated CPR, reaching an average value of 40.87–13.4 mg/L.

Pregnancy is a state of hypercoagulability, protecting the woman from bleeding during childbirth. It is known that D-dimer, a fibrin degradation product, increases during a pregnancy, reaching its maximum in the third trimester and early puerperium (22). Its prognostic value in the course of COVID-19 is confirmed by a number of studies marking not only severe cases but also such with a lethal outcome (13, 17). The D-dimer increase in our patients could potentially be a result of both the pregnancy itself and the concomitant coronavirus infection. Since there is still an absence of data on trimester-specific D-dimer values in pregnant women, its application as a diagnostic marker of the severity of the course of COVID-19 is impossible, both in our patients and in all other pregnant women.

The acid-base abnormality of respiratory origin was observed and showed respiratory alkalosis in varying degrees of compensation in 9 patients (90%), and respiratory acidosis in 1 (10%). All women were hypoxemic.

COVID-19 is a respiratory infection, characterised by the development of arterial hypoxemia, and associated with an increased alveolar-arterial oxygen gradient, which showed a ventilation-perfusion mismatch, or intrapulmonary shunting (23). The reaction of the organism to the hypoxemic conditions is manifested in the rise of minute ventilation, which leads to hypocapnia because CO2 diffuses through the tissue about 20 times faster than O2 (24). The reduction of PaCO2 increases the ratio between the bicarbonate concentration and PaCO2 and thus elevates the pH level (23). The studies show that hospitalised patients with COVID-19, initially have data on respiratory alkalosis, but when the process deepens, the development of respiratory or metabolic acidosis is observed, indicating multiorgan involvement (23, 24). In pregnant women, the growing uterus displaces the diaphragm, which decreases the functional residual capacity of the lungs, with additional increase in the oxygen need. These ventilation changes make pregnant women very sensitive to hypoxemic conditions with a subsequent quick development of respiratory alkalosis (25). In this regard, oxygen therapy in pregnant patients must be started when the values of SpO2 fall below 94% instead of 92% according to existing recommendations for non-pregnant individuals (26).

The hospital stay of all of our patients finished with preserved pregnancy. They had no indications for premature birth, and the monitoring of the fetuses did not show data of fetal distress or intrauterine retardation.

Recent research presents inconclusive data on the potential of premature birth in pregnant women with COVID-19: in part of them a high risk of birth before the term is indicated (27), while in others this risk cannot be proven (28). The studies on the fetal effects of SARS-CoV-19 in pregnant women demonstrate that the cumulative chance of fetal distress reaches 6.63%, with no congenital defects associated with COVID-19 being reported (29).

Our research was limited by the length of hospital stay and the following two check-ups, which did not allow us to fully consider the influence of SARS-CoV-19 on the last weeks of pregnancy. Currently there is no algorithm for testing babies of mothers who had COVID-19 during their pregnancy, and thus the question of vertical transmission of SARS-CoV-19 and its influence on the fetus remains unclear.

The severity of the course of COVID-19 in the patients is determined in accordance with the WHO guidelines (12). The clinical symptoms of fever, cough, and shortness of breath, as well as radiological data of saturation levels above 90%, indicate that the course of COVID-19 in these individuals was not severe. However, there is no generally available algorithm adapted towards pregnant women, making the judgment of their condition not objective enough.

CONCLUSION

The study presents a series of clinical cases of COVID-19 in pregnant women. The patients exhibited non-severe symptoms, identical to those of the general population, overlapping with pregnancy-specific symptoms. It is crucial for medical specialists to be aware of the specific laboratory changes observed during pregnancy. Due to the vulnerability of this group, the entire instrumental arsenal cannot be used for timely diagnosis and management of

COVID-19 and its complications. Safe ways to conduct imaging studies for both the mother and the fetus must be implemented. Pregnant women are more susceptible to hypoxemia during COVID-19, so oxygen therapy should be initiated earlier than in non-pregnant individuals with COVID-19. Despite concerns about the pregnancy outcome and the condition of the fetus, no long-term negative consequences of COVID-19 infection have been observed at this time. Active monitoring of pregnant patients until delivery is necessary to refine the method of childbirth and identify any possible negative neonatal outcomes associated with COVID-19.

Conflict of Interest Statement: The authors declare no conflict of interest.

Funding: The authors received no specific funding for this work.

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