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CLINICAL AND LABORATORY CHARACTERISTICS OF MILD/MODERATE COVID-19 IN PREGNANT WOMEN, BASED ON THE DURATION OF GESTATION

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ABSTRACT

The study deals with the clinical and laboratory manifestations of mild and moderate forms of COVID-19 depending on the gestational period in 69 pregnant women aged 18 to 41 (28.5 ± 6.9), hospitalized with a "COVID-19" diagnosis. The patients under study exhibited no significant differences in clinical symptoms and main laboratory data, including coagulogram ($p > 0.05$) throughout three trimesters of pregnancy. The severity of COVID-19 in pregnant women most likely depends on the presence of concomitant extragenital pathology and burdened gynecological history (pathology of previous pregnancies and childbirth) rather than on gestational period (pathology of previous pregnancies and childbirth), since more often these pathologies occurred in pregnant women with moderate COVID-19. The research showed that women in all three trimesters of pregnancy showed a significant increase ($p < 0.05$) in C-reactive protein, a specific marker of inflammation, the findings, obtained in the 2nd and 3rd trimesters of pregnancy (26.7±21.97 and 32.7±26.5 mg/l) insignificantly (p1-3 = 0.056, p2-3 = 0.231) exceeded those, observed in the 1st trimester (14.8 ± 26.9).

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Introduction

The 21st century has been facing the most urgent medical issue - COVID-19 infection [1, 2]. In a relatively short period, the pandemic has involved a majority of countries worldwide and has been challenging the healthcare systems, as well as the entire mankind [3-5].

Since the beginning of the COVID-19 pandemic, there is a growing medical awareness of the high risk of severity and deaths in patients over 60 years with concomitant diseases (cardiovascular, respiratory, renal, cancer, etc.) [6].

Pregnant women prove to be in this risk group as well because at various gestational periods the immune system undergoes changes as the fetus grows and develops. During pregnancy, the response of the monocytes and NK cells to viral antigens increases, while the number of other cells (T lymphocytes) decreases [7-9]. Besides, a pregnant woman gets more vulnerable to respiratory infections: higher concentrations of estrogen and progesterone contribute to vasomotor rhinitis and result in severe nasal stuffiness [10, 11].

However, the data on COVID-19 in pregnant women are quite contradictory. Some studies [12-18] confirm the milder course of COVID-19 in pregnant women. The authors consider the very fact of pregnancy to be the most weighty argument, as the hormones (progesterone and chorionic gonadotropin) inhibit the "cytokine storm", which is known to be an extremely serious medical condition and one of the main causes of fatal outcomes [19-22]. The results of other studies, [3, 15, 23-25] show that immunological and physiological changes in the body during pregnancy increase the susceptibility to severe infection.

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Pregnant women with novel coronavirus infection were noted to frequently develop complications such as acute respiratory distress syndrome, disseminated intravascular coagulopathy, renal failure, secondary bacterial pneumonia, and sepsis. These states often require hospitalization, treatment in the intensive care unit, and artificial lung ventilation [16, 26]. However, the characteristic features of the clinical course and laboratory changes in COVID-positive pregnant women, with regards to the gestational period, have not been sufficiently highlighted in the literature yet.

Objective: the study of the clinical and laboratory features of mild and moderate COVID-19 in pregnant women depending on the gestational period.

Materials and Methods

A retrospective review of 69 case histories of pregnant women, diagnosed and treated with mild and moderate COVID-19 from June to December 2020 in the Regional Infection Center under Ministry of Health of the Republic of Dagestan and RD State Budgetary Institution "Municipal Clinical Hospital 1", Makhachkala. (The sample did not include severe cases, since, at the peak of the pandemic, they were provided with medical care in other specialized institutions for COVID-positive pregnant women - in the maternity hospital of the Central Minicipal Hospital, Kaspiysk. The case histories were selected by continuous sampling technique.

The age of the pregnant women ranged from 18 to 41 (28.5 ± 6.9). Patients were hospitalized on the 3rd-6th day of illness, the overwhelming majority of them did not undergo any therapy.

COVID-19 was diagnosed with polymerase chain reaction (PCR) test by detecting SARS-CoV-2 RNA in the swabs taken from the oropharynx and nasopharynx (SARS-Cov-2 virus was positive in 100%).

COVID-19 clinical image and laboratory data were analyzed in all women: general and biochemical blood test, coagulogram, C-reactive protein, D-dimer, the results of instrumental studies - US of the fetus and maternal internal organs, pulse oximetry (with SpO_2 measurement to detect a respiratory failure and assess the degree of hypoxemia) and CT (computed tomography) of the chest.

The severity of COVID was assessed with consideration of the severity of general intoxication symptoms. A mild course of COVID-19 was observed in 49 pregnant women (71.0%), moderate - in 20 cases (29.0%) **(Table 2)**. Women with a mild form of the disease were observed to have subfebrile fever, the symptoms of intoxication were not expressed; those with a moderate form were observed to have increased body temperature up to 38-38.5 °C, chill, dizziness, headache, myalgia, and mild or moderate pneumonia on CT scan of the chest.

Less than half of the patients (29 cases or 42.0%) were observed to suffer from the somatic pathology: mild and moderate anemia- 12 cases, obesity -8 cases, arterial hypertension-4 case, hypothyroidism -1 case, varicose veins -2 patient, and 2 with cholelithiasis. 18 patients (26.1%) had a complicated obstetric and gynecological history, of whom 4 - infertility, 9 - spontaneous abortion in early pregnancy, and 5 - recurrent miscarriage. Concomitant diseases were more common in pregnant women with a moderate COVID-19 (in 21 out of 29 cases, or 72.4%). They had a more complicated gynecological history as well (13 out of 18 cases or 72.2%).

The characteristics of the examined groups of pregnant women are presented in **Table 1**.

Table 1. Data on the examined groups of the pregnant women

Data	Total patients	Group 1 (n=13)	Group 2 (n=16)	Group 3 (n=17)	p^{1-2}	p^{1-3}	p^{2-3}
Age	28.5±6.9	26.4±6.2	28.7±6.7	30.6±7.2	0.074	0.169	0.083
Burdened gynecological history	18	6 (33.3%)	4 (22.2%)	8 (44.4%)	0.136	0.101	0.056
Primipars	36	15 (41.7%)	12 (33.3%)	9 (25.0%)	0.084	0.218	0.073
Multiparas	33	11 (23.3%)	12 (36.4%)	10 (30.3%)	0.072	0.144	0.201
Concomitant diseases	29	9 (31.0%)	11 (38.0%)	9 (31.0%)	0.205	0.557	0.210

Note: p^{1-2} – differences between 1 and 2 trimesters, p^{1-3} – differences between 1 and 3 trimesters, p^{2-3} – differences between 2 and 3 trimesters.

Primiparas accounted for 36 (52.2%) and multiparous - 33 (47.8%). Depending on the gestation period (according to the history and ultrasound of the fetus), pregnant women were divided into 3 groups: 1st group - the first trimester of pregnancy (up to 13 weeks) - 26 (37.7%) pregnant women;

2nd group - the second trimester of pregnancy (14-27 weeks) - 23 (33.3%) pregnant women;

Group 3 - the third trimester of pregnancy (from 28 to 40-42 weeks) - 20 (29.0%) pregnant women.

The groups under study were comparable in terms of age, the burden of obstetric and gynecological history, presence or absence of gynecological and somatic pathology the pregnancy was associated with, and severity of COVID-19 **(Tables 2 and 3)**.

The results were statistically analyzed with the Biostat 10 and Microsoft Office Excel programs with obtaining the arithmetic mean, its deviation, and fractional values. The significance of changes in mean values was assessed with the parametric Student's t-test for independent groups. Differences were considered statistically significant at $p < 0.05$.

Results and Discussion

Out of the total number, analyzed in an epidemiological anamnesis, 14 pregnant women (20.3%) had been in contact with COVID patients, 55 women (79.7%) denied contact with the infected people.

Analysis of the severity of COVID-19 by trimester of pregnancy is presented with the following data: in the first trimester, the viral infection was proved to be mild in 20 cases (40.8%), and moderate in 8 cases (40.0%), in the second trimester of pregnancy - 16 cases (32.7%) were found to have a mild form and 6 cases (30.0%) - a moderate form of the disease. In the third trimester of pregnancy, the mild form was found in 13 women (26.5%) and the moderate form - in 6 (30.0%).

The most common clinical symptoms in the patients under study: cough (dry or with a small amount of sputum) (in 71.0%), reduced olfaction and gustation (in 55.0%), stuffiness in the chest (in 39.1%), and dyspnea (37.6%). 62 cases (89.9%) were associated with rise in body temperature: subfebrile fever - in 37 (53.6%), febrile - in 20 (29.0%), and hectic - in 5 (7.2%) **(Table 3)**. Such clinical symptoms as cough, reduced olfaction and gustation, and stuffiness in the chest were often diagnosed throughout all three trimesters of pregnancy. In the 1st trimester, 75.0% of the pregnant women developed cough, 53.6% - reduced olfaction and gustation, 39.3%- stuffiness in the chest, 68.2%, 63.6% in the 2nd trimester, respectively. 40.9%, in the third trimester - respectively in 68.4%, 47.4% and 36.8%. The temperature was subfebrile in the majority of cases - in the 1st, 2nd, and 3rd trimesters, respectively, in 57.1%, 59.1.6%, and 47.4%. There were no significant differences in the frequency of clinical symptoms by trimesters (p> 0.05).

Table 2. Clinical presentation of COVID-19 depending on gestational period

Clinical manifestations	Total number n = 69	Group 1 n = 28	Group 2 n = 22	Group 3 n = 19	p^{1-2}	p^{1-3}	p^{2-3}
Cough	49 (71.0%)	21 (75.0%)	15 (68.2%)	13 (68.4%)	0.125	1.246	0.389
Dyspnea	26 (37.6%)	8 (28.6%)	7 (36.8%)	11 (57.9%)	0.114	0.041	0.582
Stuffiness in the chest	27 (39.1%)	11 (39.3%)	9 (40.9%)	7 (36.8%)	0.068	0.032	0.127
Rhinorrhea	10 (14.3%)	4 (14.3%)	3 (13.6%)	3 (15.8%)	0.309	0.153	0.784
Headaches	14 (20.3%)	6 (21.4%)	5 (22.7%)	3 (15.8%)	0.031	0.024	0.165
Myalgia	10 (14.3%)	4 (14.3%)	3 (13.6%)	3 (15.8%)	0.031	0.024	0.165
Decrease in olfaction and gustation	38 (55.0%)	15 (53.6%)	14 (63.6%)	9 (47.4%)	0.056	0.067	0.812
Sore throat	16 (23.2%)	2 (3.4%)	5 (22.7%)	9 (47.4%)	0.051	0.052	0.016
Diarrhea	8 (11.6%)	2 (7.1%)	3 (13.6%)	3 (15.8%)	0.163	0.043	0.58
Fever *Subfebrile, febrile, hectic*	37 (53.6%) 20 (29.0%) 5 (7.2%)	16 (57.1%) 8 (28.6%) 1 (3.6%)	12 (54.5%) 7 (31.8%) 2 (9.1%)	9 (47.4%) 5 (26.3%) 2 (10.5%)	0.087 0.324 0.073	0.076 0.144 0.093	0.052 0.365 0.168

Note: p^{1-2} – differences between trimesters 1 and 2, p^{1-3} – differences between trimesters 1 and 3, p^{2-3} – differences between trimesters 2 and 3.

The prompt and timely diagnosis of COVID-19-associated pneumonia in pregnant women is of particular importance since the above complication can be asymptomatic, increasing thus the risk of adverse outcomes in both mother and fetus. Of the total number of pregnant women with COVID-19, chest CT was performed in 57 women (82.6%) (18 in the 1st trimester, 20 in the 2nd trimester, and 19 in the 3rd trimester of pregnancy). 20 (35.1%) of them were diagnosed with bilateral pneumonia (damage to pulmonary tissue - CT-1, CT-2), the rest of the cases did not show lung involvement. Most often, pneumonia developed in the 3rd trimester of pregnancy -in 8 patients (6 women fell ill with a moderate form of pneumonia, the mild course was observed in 2 patients). In the 1st trimester of pregnancy, pneumonia was detected in 7 women (5 cases of moderate form, 2 of the mild), in the 2nd trimester - in 5 women (4 cases of moderate form, 1 of the mild). All 15 patients with moderate pneumonia (5 in the 1st trimester, 4 in the 2nd trimester, and 6 in the 3rd trimester) had signs of grade I-II respiratory failure (blood saturation index> 93%), the rest of the patients showed no signs of respiratory failure.

It should be noted that general and biochemical blood samples of COVID-positive patients have been referred to non-specific diagnostic methods. Nevertheless, the tests play an important role in assessing the disease severity and prognosis (including the outcome) and allow adjusting the treatment modes. The main laboratory data in the studied groups upon admission to the hospital are presented in **Table 3**.

Table 3. Main laboratory data in pregnant women of the studied groups

Data	Group 1 (n=13)	Group 2 (n=16)	Group 3 (n=17)	p^{1-2}	p^{1-3}	p^{2-3}
Hemoglobin, gr/l	129.6±17.2	112.7±15.8	106.4±15.1	0.132	0.036	0.579
Red blood cells, 1012/l	4.28±0.59	3.74±0.53	3.93±0.33	0.006	0.075	0.370
White blood cells, 109/l	9.11±3.94	7.68±2.49	9.05±3.25	0.182	1.024	0.367

Blood platelets, 109/l	238.0±53.23	205.4±50.84	229.9±63.74	0.194	0.089	0.648
C-reactive protein, mg/l	14.8±6.9	21.97±6.7	26.5±4.7	0.067	0.056	0.231
Procalcitonin, ng/ml	0.027±0.1	0.03±0.1	0.23±0.01	0.384	0.076	0.428
Total bilirubin, μmol/l	8.3±2.3	7.9±2.7	10.1±2.6	0.036	0.334	0. 737
Ferritin, mkg/l	17.91± 12.7	50.4±1.3	48.9±17.2	0.580	0.072	0.549
Cholesterol, mmol/l	5.2±0.5	5.3±0.6	5.1±0.5	0.058	0.069	0.097
Glucose, mmol/l	4.6±9.6	4.27±1.0	3.7±0.5	0.145	0.233	0.076
alanine aminotransferase (ALT), u/l	20.4±11.7	26.2±12.2	25.1±11.5	0.118	0.230	0.071
aspartate aminotransferase (AST), u/l	27.0±9.4	31.5±13.1	29.2±9.7	0.123	0. 603	0.597
alkaline phosphatase (AP), u/l	122.1±21.2	134.5±29.2	130.2±25.2	0.119	0.051	0.463
Total protein, g/l	72.8±11.9	66.5±12.2	64.8±6.3	0.107	0.084	0.204
Creatinine, μmol/L	54.2±13.5	58.4±14.7	60.8±20.7	0.093	0.078	0.576
Urea, mmol/l	7.3±4.3	7.7±5.1	6.9±4.5	0.107	0.166	0.389
D-dimer, ng/ml	481.8±71.4	462.9±39.1	446.1±71.5	0.063	0.267	0.506
activated partial thromboplastin time (APTT), sec	33.5±25.4	36.8±17.4	37.3±26.6	0.252	0.075	0.562
protombine index (PTI), %	120±17.4	116.2±20.2	112.7±23.4	0.092	0.146	0.085
Fibrinogen, gr/l	3.8±1.2	4.2±2.6	4.3±2.9	0.246	0.339	0.072

Note: p^{1-2} – differences between trimesters 1 and 2, p^{1-3} – differences between trimesters 1 and 3, p^{2-3} – differences between trimesters 2 and 3.

The data in the table show that most of the laboratory parameters in COVID-positive pregnant women did not vary significantly throughout the pregnancy trimesters (p> 0.05). The data show a significant decrease (p <0.05) in blood hemoglobin in the 2nd and 3rd trimesters of pregnancy (112.7 ± 15.89 g/l and 106.4 ± 15.19 g/l, respectively), compared with the 1st trimester (129.6 ± 17.28), which may be due to initial anemia prior to SARS-Cov-2 (out of 12 cases of anemia, 6 occurred in the 3rd trimester and 4 in the 2nd trimester). Women in all three trimesters of pregnancy showed a significant increase (p <0.05) in C-reactive protein, a specific marker of inflammation, the findings, obtained in the 2nd and 3rd trimesters of pregnancy (21.97 ± 26.7 and 26.5 ± 32, 7 mg/l) insignificantly (p1-3 = 0.056, p2-3 = 0.231) exceeded those, observed in the 1st trimester (14.8 ± 26.9). Other laboratory findings, including coagulogram (APTT, PTI, fibrinogen) and D-dimer, remained normal, this confirms that the patients under study were affected with a non-severe form of COVID-19 and the data did not vary significantly between the groups (p> 0.05).

Conclusion

The analysis of clinical manifestations and basic laboratory data in pregnant women with mild to moderate COVID-19 did not reveal significant differences depending on the gestational period. In all the three trimesters of pregnancy, patients were most often diagnosed with such clinical symptoms as fever, cough, decrease in olfaction and gustation, and stuffiness in the chest; however, no significant differences were recorded in the frequency of clinical symptoms, including basic laboratory findings, by trimester (p >0.05). The severity of COVID-19 in pregnant women most likely depends on the presence of concomitant extragenital pathology and burdened gynecological history (pathology of previous pregnancies and childbirth) rather than on gestational period, since more often, these pathologies occurred in pregnant women with moderate forms COVID-19.

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