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Impact of COVID-19 disease on obstetric outcomes in the third trimester of pregnancy

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ABSTRACT

Objectives: The aim of this study is to evaluate the effect of coronavirus disease 2019 (COVID-19) diagnosed in the third trimester of pregnancy on maternal, fetal, and obstetric outcomes.

Methods: This retrospective study included 109 pregnant women hospitalized with a diagnosis of COVID-19 during the third trimester of pregnancy (28-40 weeks) in a tertiary center between March 1 and December 31, 2020. Demographic characteristics, clinical signs, and obstetric outcomes of the patients were searched for analysis. Laboratory and x-ray results were reported, and treatment methods were summarized. Finally, mother-newborn results were recorded.

Results: We included one hundred nine pregnant women in this study. We divided the patients into two groups as those with positive PCR test (n = 59) and negative PCR test and possible covid patients (n = 50) whose symptoms and histories meet the covid criteria. The mean age of the patients was 28.90 ± 6.21 years, and the mean week of gestation was 37.45 ± 2.29 weeks. Half of the patients were asymptomatic (n = 57, 47.7%), and 69% of all patients were delivered by cesarean section. The hospitalization time of antigen-positive cases was between 2-9 days. The mean lymphocyte count was 1.37 ± 0.45 ×103/mL in the PCR positive patient group, and this value was 1.67 ± 0.54 103/mL in the PCR negative patients ($p = 0.007$). While the mean neutrophil count was 8.13 ± 3.16 × 103/mL in the PCR positive patient group, this value was 10.99 ± 4.14 × 103/mL in the PCR negative patients ($p < 0.001$). Fifteen patients required intensive care unit follow-up, and 2 of them died while receiving mechanical ventilator support.

Conclusions: COVID-19 infection in the third trimester of pregnancy does not affect fetal and maternal outcomes if the disease is under control at an early stage. In hospitalized patients, symptoms are more precious than antigen testing.

Keywords: COVID-19, pregnancy and SARS CoV-2, prenatal diagnosis, third trimester

The new type of Coronavirus (COVID-19) has been defined as a deadly pandemic that spread to the world from Wuhan, China at the end of 2019, transmitted to a large number of people [1]. In January 2020, the World Health Organization (WHO) listed the new coronavirus pneumonia epidemic as a public health emergency of international concern. WHO defined the disease as "COVID-19" and the causative virus as "Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)" in March 2020 [2].

The incidence of adverse events caused by COVID-19 during pregnancy appears to be lower than

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previously reported rates for MERS and SARS infections, the same applies to maternal deaths: While the mortality rate in pregnant women affected by SARS and MERS varies between 25% and 30% [3, 4], the maternal mortality rate associated with COVID-19 is around 2% [5].

Due to physiological changes in the immune and cardiopulmonary systems, pregnant women are particularly susceptible to respiratory pathogens and severe pneumonia (for example, diaphragmatic elevation, increased oxygen consumption, and edema of the airway mucosa), which may render them intolerant to hypoxia [6]. Today, the clinical course of pregnant women diagnosed with COVID-19, delivery process, maternal and fetal outcomes are still important questions. Previous studies have reported high rates of adverse pregnancy outcomes such as preterm labor, premature rupture of membranes (PROM), and cesarean delivery (C/S) in pregnant women with COVID-19 infection [7, 8]. Therefore, pregnant women and their newborns should be considered as potential risk groups in the current COVID-19 pandemic.

The virus is mainly transmitted by respiratory droplets and/or contact [9]. The majority of patients (80%) present with a mild or asymptomatic clinical condition. Approximately 15% of them present with fever, cough, and shortness of breath, respiratory distress, and pneumonia. Approximately 5% of the patients require intensive care and respiratory support units due to 'Serious Acute Respiratory Syndrome' and multi-organ failure [10]. Laboratory findings usually include lymphopenia, thrombocytopenia, and abnormal liver enzymes [11]. Pneumonia is the most common serious symptom of infection and is usually seen with bilateral infiltration on thoracic imaging. Typical ground-glass opacities are seen in 56.4% of cases on computed tomography. Radiological findings are not seen in 17.9% of mild cases [12].

Diagnosis is based on the exposure history, clinical symptoms, laboratory test results, X-ray imaging findings, and a positive real-time reverse transcription-polymerase chain reaction (RT-PCR) result for COVID-19. RT-PCR test is the current gold standard for identifying SARS-CoV-2 from respiratory specimens with suspected COVID-19 patients [13].
The purpose of this article is to analyze the maternal, fetal, and obstetric outcomes of pregnancies diagnosed with COVID-19 in the third trimester [14, 15].

METHODS

This retrospective study was carried out on 109 pregnant women who were followed-up for COVID-19 infection in the third trimester (28-40 weeks) in a tertiary center and were treated in the hospital and then delivered in the same hospital. Fifty-nine of the patients were diagnosed as COVID-19 with positive PCR test and other fifty patients were defined as possible COVID-19. For the possible and confirmed Covid-19 diseases definition, the approaches of the World Health Organization and the Ministry of Health of the Republic of Turkey were accepted as a reference. The patients were diagnosed with COVID 19 infection based on real-time polymerase chain reaction (RT-PCR), pulmonary tomography results, and/or clinical status.

Bursa Yüksek İhtisas Training and Research Hospital ethics committee approved this study with numbered 2011-KAEK-25 2022/11-15, and informed consent was obtained for the study. The demographic, clinical characteristics, treatments, and obstetric outcomes of the patients were recorded by the researchers through patient files and hospital records. Eligibility criteria included laboratory-diagnosed COVID-19, third-trimester pregnancy at presentation. Pregnant women whose pregnancy follow-up or delivery data could not be obtained were excluded from the study.

Statistical Analysis

Statistical analyses were performed using SPSS version 23 (IBM Corp, Armonk, NY, USA). Mean or median values were used for descriptive variables according to data. Numbers and percentages were used for categorical data. The patients were grouped according to their PCR results. Shapiro Wilk test was used to determine the distribution and Mann Whitney U, or chi-square tests were applied to determine the differences between the groups. $P < 0.05$ was considered significant.

RESULTS

In Table-1, we presented the demographic and clinical

Table 1. Clinical characteristics and obstetric outcomes of groups

	COVID PCR positive n = 59	COVID PCR negative n = 50	*p value*
Age (years)	29.13 (6.49)	28.64 (5.93)	NS
BMI (kg/m^2)	27.98 (4.35)	27.85 (3.37)	NS
Gestational age (weeks)	37.50 (2.17)	37.40 (2.45)	NS
Route of delivery, n (%)			
Vaginal	17 (28.8)	16 (32.0)	NS**
C-section	42 (71.2)	34 (68.0)	
Pregnancy complications, n (%)			
Absent	43 (72.9)	37 (74.0)	NS**
Present	10 (16.9)	13 (26.0)	
Birth weight (g)	3039.79(585.66)	2942.40(654.48)	NS
Apgar score*			
1st min.	9 (0-9)	9 (6-9)	NS
5th min.	10 (0-10)	10 (8-10)	NS
Length of hospitalization (days), median (min-max)	5 (2-9)	5 (1-7)	**0.04**
Laboratory parameters			
Hemoglobine (g/dL)	10.99 (1.78)	10.68 (1.46)	NS
WBC (×10^9/L)	9.93 (3.59)	13.39 (4.19)	**< 0.001**
Lymphosyte (×10^3/mL)	1.37 (0.45)	1.67 (0.54	**0.007**
Neutrophil (×10^3/mL)	8.13 (3.16)	10.99 (4.14)	**< 0.001**
Platelets (×10^9/L)	220.59 (75.83)	248.22 (81.24)	NS
C-reactive protein (mg/L)	32.51 (35.19)	32.84 (37.07)	NS
D-dimer (µg/mL)	4.59 (10.37)	4.27 (7.54)	NS
Fibrinogen (mg/dL)	447.40 (109.18)	482.50 (115.17)	NS
Prothrombine Time (seconds)	11.44 (1.03)	11.27 (0.79)	NS
aPTT (seconds)	25.83 (4.49)	23.06 (3.22)	**0.001**
Troponin -T (ng/mL)	7.85 (21.92)	5.61 (6.30)	NS
Creatine kinase (ng/mL)	226.46 (281.67)	230.32 (365.65)	NS
FBG (mg/dL)	84.18 (25.08)	81.70 (13.41)	NS
AST (IU/L)	28.07 (19.69)	26.75 (17.23)	NS
ALT (IU/L)	17.77 (14.58)	14.55 (11.46)	NS
LDH (IU/L)	300.66 (257.52)	297.54 (98.43)	**0.03**
BUN (mg/dL)	19.49 (14.65)	16.09 (6.31)	NS
Creatinine (mg/dL)	0.56 (0.22)	0.50 (0.14)	NS

Data are given as mean (standard deviation) or median (min-max). WBC = white blood cell, aPTT = activated partial thromboplastin time, IU = international unit, FBG = fasting blood glucose, ALT = alanine aminotransferase. AST = aspartate aminotransferase, LDH = lactic dehydrogenase, BUN = blood urea nitrogen, NS = non-significant. *Mann Whitney U test, **Chi-square

characteristics of the patients. The mean age of all pregnant women was 28.9 ± 6.2 years. The mean week of delivery was 37.4 ± 2.3 weeks. Almost half of the patients were asymptomatic (n = 57, 47.7%). Computed tomography was performed on 41 patients, and 18 had severe involvement. Nineteen (17.5%) of the patients had severe disease, while 15 were followed in the intensive care unit, two patients died. Neonatal SARS CoV-2 was detected in only one baby. Preterm delivery and premature rupture of membranes were the most common pregnancy complications. Placental abruption developed in 5 patients. While the number of complications we have stated in the second table is 23, this number is seen as 40 in the first table. This difference is reflected in the fact that there is more than one complication in the same patient. All analysis is available in Table 1.

In Table 2, we analyzed the laboratory parameters and obstetric results of pregnant women with a diagnosis of COVID-19. In addition, we divided these patients into two groups with and without positive PCR tests and presented the analyzes.

The mean age of PCR-positive patients was 29.13 ± 6.49 years, while the mean age of PCR-negative patients was 28.64 ± 5.93 years. While 33 (30.2%) of 109 patients in the study delivered vaginally, the cesarean section rate of the other population was around 50% in the same period. The mode of delivery did not differ significantly between the two groups. While only 23 (21.1%) of all patients had pregnancy-related complications, this situation was not statistically different between the two groups with and without PCR positive (Table 2).

While the white blood cell count was 9.93 ± 3.59 ×109/L in the PCR positive patient group, it was 13.39 ± 4.19 ×109/L in the PCR negative patient group, and the situation differed between the two groups ($p < 0.001$). While the lymphocyte count was 1.37 ± 0.45 ×103/mL in the PCR positive patient group, this value was 1.67 ± 0.54 ×103/mL in the PCR negative patients, which was significant ($p = 0.007$). While the neutrophil count was 8.13 ± 3.16 ×103/mL in the PCR positive patient group, this value was 10.99 ± 4.14 ×103/mL in the PCR negative patients, which was significant ($p < 0.001$). Active partial thromboplastin time was significantly different in both groups ($p = 0.001$). While it was 25.83 ± 4.49 seconds in the PCR positive patient group, it was 23.06 ± 3.22 seconds in the neg-

Table 2. Demographic and clinical characteristics of patients (n = 109)

Variables	Values
Maternal age (years)	28.90 ± 6.21
Gestational age at delivery (weeks)	37.45 ± 2.29
Initial symptoms	
Asymptomatic	52 (47.7)
Symptomatic	57 (52.2)
Fever	24 (22.2)
Cough	23(21.1)
Headache	20 (18.3)
Sore throat	5 (4.5)
Dyspnea	18 (16.5)
Myalgia	6 (5.5)
Computed tomography (pulmonary)	
Normal	11 (10)
Pneumonia	12 (11)
Ground glass opacities	18 (16)
COVID-19 severity	
Mild	66 (60.6)
Moderate	24 (22.1)
Severe	19 (17.5)
Respiratory support	
Nasal oxygen therapy	10 (9.1)
High flow nasal cannula	8 (7.4)
Invasive mechanic ventilation	2 (1.9)
Route of delivery	
Vaginal	33 (30.3)
C-section	76(69.7)
Cesarean indications	
Previous cesarean delivery	33 (43.4)
Fetal distress	22 (28.9)
Cephalopelvic disproportion	6 (9.2)
Placenta previa	3(3.9)
Malpresenation	4(5.3)
Hypertension-Preeclampsia	6 (7.9)
Intrauterine exitus	2(1.9)
Pregnancy complications	
Gestational diabetes mellitus	2 (1.8)
Preeclampsia	6 (5.5)
Preterm delivery	17 (15.6)
Preterm rupture of membranes	10 (9.1)
Placental abruption	5 (4.6)
Neonatal Sars COv 2 positivity	1 (1)
Admission to NICU	15 (13.8)
Maternal mortality	2 (1.8)

Values are given as mean ± standard deviation or n (%).

ative patient group (Table 2). We present the complete analysis in Table 2.

DISCUSSION

This article represented the clinical findings, labor outcomes, obstetric outcomes, and pregnancy complications of hospitalized pregnant women due to SARS CoV-2 positivity in the third trimester of pregnancy. We also attempted to compare the PCR positive and negative of the disease with these outcomes.

In the present article, pregnant women who caught COVID-19 in the third trimester of pregnancy, in general, have a mild to moderate course of the disease. Whether the PCR result is positive or not, it is primarily uncomplicated. While approximately 70% of the patients delivered by cesarean section, most of these were due to COVID-19 unrelated reasons. Acute fetal distress developed in 20% of the pregnant women, but it was not unusual to determine their direct relationship with covid-19. Intrauterine fetal death occurred in 2 patients, but they were not neonatal SARS CoV-2. Although blood white blood cell, neutrophil, lymphocyte, aPTT, and LDH values were significantly different between PCR positive or negative groups, these values were not meaningful in pregnancy management.

In their study, Mahajan NN *et al*. reported the pregnancy complications due to first wave COVID-19 infection as 60.9%, while the complication rate due to the second wave was 72.2% [16]. Gajbhiye *et al*. [17] reviewed 441 cases and presented them as articles. Accordingly, preterm birth developed in 26% of the cases, fetal distress in 8% and premature rupture of membranes in 9% of cases. The most common comorbidities associated with pregnant women with COVID-19 were hypertensive disorders (10%), diabetes (9%), placental disorders (2%), coinfections (3%). Premature birth (25%), respiratory distress syndrome (8%), pneumonia (8%) were reported among newborns of COVID-19 mothers. In the article they published with a large patient group, Sun *et al*. [18] pointed out the complicated conditions of pregnancy that increased during the COVID-19 period. Accordingly, the most common adverse outcome in 152,903 deliveries examined during the COVID-19 pandemic period were premature rupture of membranes (10.3%), gestational diabetes (9.3%), and gestational hypertension (8.5%). Compared to the reference period, the pandemic period was characterized by statistically significantly higher rates of gestational diabetes, gestational hypertension, poor fetal growth, and preeclampsia.

Due to the vulnerable immune system of pregnant women, mothers and newborns are one of the weakest populations in pandemics [19]. There is insufficient literature on the approach and potential adverse effects of COVID-19 in different pregnancy trimesters [20-22]. Ideal pregnancy management in the COVID-19 pandemic is essential because pregnant women are at higher risk for a worsening clinical course, increased pregnancy complication rates, the efficacy of medications, the optimal delivery route, the safety of breastfeeding, and the risk of vertical transmission [23, 24]. The effectiveness of drugs, the optimal delivery route, the safety of breastfeeding, and the risk of vertical transmission are still controversial [25, 26].

According to our study, almost half of the pregnant women were asymptomatic. Those had generally mild symptoms. There were eighteen pregnant women describing dyspnea, and we had to start invasive mechanical ventilation for only two pregnant women. As mentioned above, the effects of COVID-19 infection in pregnant women are still controversial, and more extended studies are needed to understand the immune response. We provided mechanical ventilator support to 2 of the 15 patients we took to the intensive care unit, but both died. Considering this situation and the rate of asymptomatic patients, we assume that the progression of the disease is prevented at an early stage in terms of prognosis.

This study can claim that the mode of delivery is not affected by COVID-19 infection during the third trimester of pregnancy by looking at cesarean section indications. We also think that it is not related to neonatal SARS CoV-2. We also consider that it is not associated with neonatal SARS CoV-2.

According to the antigen test, there were no significantly different delivery modes or pregnancy complications in the definite and probable case groups. In this context, we should organize the follow-up and treatment of the pregnant according to the course of the disease, not the PCR antigen test. Keeping the disease under control at an early stage is the most critical factor, and it is still unclear at what stage and to what

extent the fetus will be affected.

Limitations

This study has some limitations. We could not report the final status of the infants and whether they had long-term diseases. Furthermore, it would be helpful to mention the mothers' long-term outcomes, the result of the disease, and its possible complications in more prolonged periods. On the other hand, there were also some limitations related to the data about the mother, like the starting and duration date of COVID-19 and vaccination status. However, this study supplied some critical information associated with the perinatal and neonatal results of COVID-19, and future well-designed meta-analyses can improve the awareness of this disease.

CONCLUSION

In conclusion, COVID-19 infection present in the third trimester of pregnancy may not affect pregnancy and delivery outcomes if the disease is under control at an early stage. Management may be more accurate in hospitalized patients based on patient symptoms than antigen testing.

Authors' Contribution

Study Conception: FB; Study Design: SSK; Supervision: SSK; Funding: FB; Materials: SSK; Data Collection and/or Processing: SSK; Statistical Analysis and/or Data Interpretation: FB; Literature Review: SSK; Manuscript Preparation: SSK, FB and Critical Review: SSK.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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