Obstetric Patients with Coronavirus Disease: Symptoms, Critical Illness and Mortality

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ARTICLE INFO	ABSTRACT
Article type: Original article *Article History:* Received: 16-Jul-2022 Accepted: 30-Oct-2022 *Key words:* COVID-19 Coronavirus Pregnancy Mortality	*Background & aim:* Infection with COVID-19 during pregnancy increased some of the complications such as preterm labor, Intensive Care Unit (ICU) admission, maternal mortality, and adverse neonatal outcomes. The aim of the present study was evaluation of symptoms, critical illness, and mortality among pregnant patients with COVID-19 in Mashhad, North East Iran. *Methods:* This descriptive retrospective study included pregnant women with COVID-19 diagnoses referred to one of the teaching hospitals in Mashhad between February 20, 2020, and September 21, 2022, using census method. The patients were stratified into symptomatic mild, moderate, and severe cases, according to the classification of National Institute of Health (NIH), USA. Data analysis was done using SPSS 26 by Student's t-test, logistic regression, and chi-square test. *Results:* Out of 460 pregnant women, sixteen symptoms were reported by the patients with dyspnea being the most frequent. Cough, fever (P= 0.00), abdominal pain (P= 0.04), and chills (P= 0.03) were significantly more frequently observed among the ICU-admitted patients. The least common symptom was flank pain. Women with severe disease who died were at significantly higher risk for fever, cough, and dyspnea. 116 (25.2%) cases had severe disease and were admitted to the ICU and 5.7% expired. Hospitalization in the ICU was the most important predictor of death (B=-22.286, P=0.00). *Conclusion:* The study indicates that pregnant women who experience symptoms such as fever, dyspnea, cough, chills, or abdominal pain are more susceptible to severe COVID-19.

Introduction

The COVID-19 coronavirus pandemic was first discovered in Wuhan, China, in December 2019. As of January 2019, it has affected more than 500 million people worldwide and caused the deaths of over 6 million people (1-2). Similar to numerous other medical conditions, this illness is accompanied by various symptoms, such as fever, cough, sore throat, and gastrointestinal discomfort. Moreover, it has been demonstrated to exhibit similarities with multiple other

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conditions (3-4). Furthermore, the results of the study on COVID-19 encompass a spectrum of manifestations, spanning from mild illness to requiring intensive care unit admission and ultimately resulting in a fatality. According to previous studies, China has reported a mortality rate of 2. 3%, whereas Italy has reported a higher mortality rate of 26% (5).

The prevalence of severe disease is significantly higher among certain populations, such as the elderly, individuals with chronic diseases such as diabetes, and pregnant women (6-7). Women who are pregnant have a greater risk of more severe diseases for an array of reasons. Several factors are associated with the susceptibility to and severity of SARS-COV2 infection. Firstly, there is an elevation in the diaphragm and an escalated demand for oxygen (8-9). Additionally, there is an upregulation of ACE2 receptor expression, which facilitates the infiltration of SARS-COV2 into cells. Furthermore, the upper respiratory tract undergoes inflammation leading to swelling (10-11). It must be noted, however, that physiologic changes that occur during pregnancy make the diagnosis of COVID-19 challenging. Several metanalyses confirmed that infection with COVID-19 during pregnancy increased some of the complications such as preterm labor Intensive Care Unit (ICU) admission, maternal mortality, and adverse neonatal outcome (12-13).

Other studies that so showed that pregnant patients with COVID-19 demonstrated an increased risk of some complications, such as preterm birth, preeclampsia, ICU admission, and stillbirth (14-15). In another study, preterm delivery is the most common detrimental pregnancy outcome in COVID-19-positive pregnant patients (18). The rate of mortality in pregnancy is different between studies from 1.35% to 12.3% (16-18).

"In Iran, on February 19, 2020, two patients in Qom City, Central Iran, had their SARS-CoV-2 positivity confirmed". The epidemic then soon spread to other near provinces and shortly thereafter in all 31 provinces of the country. By March 8, 2020, the spokesman for the Ministry of Health and Medical Education, reported that 194 individuals had died from COVID-19 and that 6,566 people had tested positive for SARS-Cov-2 overall" (19).

The current study attempted to assess the clinical attributes of COVID-19 in the context of pregnancy, with a specific focus on Iran. It was motivated by the insufficiency of previous research in presenting an accurate of the symptoms and severity of the disease in pregnant individuals. This research aimed to examine the characteristics of obstetric patients afflicted with the coronavirus disease, including the manifestation of symptoms, critical illness, as well as mortality rates in Mashhad, North East Iran.

Materials and Methods

This descriptive retrospective study involved the recruitment of patients from Imam Reza Hospital in Mashhad, Iran an esteemed super-specialty and teaching hospital in North East Iran. This study encompassed all pregnant individuals referred to Imam Reza Hospital, within the time frame of February 20, 2020, to September 21, 2022, who were diagnosed with COVID-19 based on positive results obtained from polymerase chain reaction (PCR) testing of nasopharyngeal or nasal swabs or detection of abnormal findings from high-resolution computed tomography (HRCT) scans. Sampling was by census method.

The study excluded pregnant women who had negative PCR results and normal HRCT scans.

The laboratory and imaging departments of the hospital performed the testing by using polymerase chain reaction (PCR) of nasopharyngeal or nasal swabs or high-resolution computed tomography (HRCT). Throughout the entire period of the study, the subjects received regular care and treatment for COVID-19. All participants were required to fill out a consent form during the enrollment process and were allowed to leave the study at any time. The patients' information was extracted from their medical records.

All the pregnancy patients with COVID-19 diagnosis were admitted in a special section by census method, which separated them from other pregnant women. Patients were transferred to the ICU if their conditions deteriorated and progressed into severe diseases. The patient's vital signs and COVID-19 symptoms were recorded daily on standard

collection sheets. Furthermore, a qualified obstetrician performed regular monitoring of the subjects' clinical observations and provided appropriate obstetric care as necessary. Sonographic examinations were conducted according to a predetermined schedule to closely assess and observe fetal well-being. The questionnaire included age, height, weight, blood pressure and laboratory tests . The validity of the check lists was confirmed by ten members of the academic staff of the University of Medical Sciences. Two study investigators independently reviewed the data collection tools to verify the data accuracy.

The patients were stratified into asymptomatic/mild and moderate/severe cases based on the established criteria provided by the National Institute of Health (NIH). Mild symptoms include fever, cough, sore throat, myalgia, and anosmia, as well as symptoms of nausea and vomiting. Severe symptoms like the above with dyspnea required advanced oxygen support and admission to the ICU. In the present study, the entirety of the individuals under examination were admitted to both the gynecology ward and the Intensive Care Unit (ICU) at Imam Reza Hospital. Patients with mild symptoms who were managed in an outpatient setting were excluded from the study.

The data analysis was conducted using SPSS version 26. Measures of central tendency and dispersion were used to characterize the variables. Quantitative data in two groups of patients, moderate and severe patients were compared using the Student's t-test, while qualitative data were analyzed using the Chi-square test. It was determined that the significance criterion was P< 0.05.

Results

A total of 460 pregnant women with confirmed COVID-19 were included in the present study. In the current cohort, the average age of the patients was 30.81±6.2 years and the gestational age (GA) was 29.7±8.3 weeks.

Table 1. The demographic data and mean of vital signs of the study population

Variable	Non-ICU Admission N=334 (M±SD)	ICU Admission N=116 (M±SD)	P - Value
Age	30.68±6.23	31.19±6.21	0.448
BMI	28.29±4.94	27.91±5.54	0.630
Systolic blood pressure	112.69±12.57	116.08±15.53	0.054
Diastolic blood pressure	70.49±10.02	72.77±11.37	0.063
Pulse rate	96.32±14.29	101.27±18.20	0.016
O2 saturation	94.97±3.16	88.79±8.04	< 0.001
Respiratory rate	22.80±10.95	25.40±7.36	0.032
Gestational age	29.09±8.68	27.68±7.29	0.176
Hemoglobin	11.60±1.36	11.28±1.58	0.037
HCT	35.50±3.57	34.60±4.87	0.072
Platelet	182.08±45.60	189.69±49.89	0.374
White Blood Cells	18.17±8.90	20.62±11.89	0.08
Lymphocytes	18.96±3.13	15.64±11.89	0.005
AST	55.23±103.26	77.21±107.73	0.158
ALT	59.07±84.28	81.39±91.68	0.031
Creatinine	1.47±2.12	1.55±2.38	0.744
ESR	45.03±21.65	50.57±29.80	0.119
CRP	52.62±48.56	84.55±57.12	< 0.001
Ferritin	156.25±159.12	239.83±180.22	0.007
PT	11.27±1.28	11.43±1.92	0.366
PTT	30.41±16.49	32.45±18.28	0.322
FBS	90.79±23.18	104.89±34.89	< 0.001
D Dimer	2328.86±1750.40	2931.91±2248.17	0.108
LDH	490.97±277.14	821.70±1008.83	0.002

Intensive Care Unit (ICU)

The full demographic and vital signs of the study population are shown in Table 1.

Furthermore, Out of the total number of participants examined, 116 individuals (25. 2%) exhibited severe disease symptoms and consequently required admission to the intensive care unit. Additionally, a mortality rate of 5. 7% was observed within the examined group. The average age, body mass, gestational age, and diastolic blood pressure did not significantly differ between the two groups of deceased and discharged patients (P > 0.05). However, four important symptoms that determined the deterioration of the patients include: systolic blood pressure, pulse rate and respiratory rate, and O2 saturation were significantly different in the two groups (P<0.05, Table 1). Women who were admitted to ICU had higher respiratory rates (P=0.032). Additionally, these patients had lower lymphocyte levels (P=0.005), higher hemoglobin levels (P=0.037), and higher CRP levels (P<0.001) compared to non-ICU patients. This study also found that there were no significant differences between patients admitted to the ICU and those in non-ICU settings regarding variables such as age, body mass index (BMI), weight, height, gestational age, systolic and diastolic blood pressure, platelet levels, white blood cell counts, aspartate transaminase (AST) levels, alanine transaminase (ALT) levels, creatinine levels, erythrocyte sedimentation rate (ESR), prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR), and D-Dimer levels.

Table 2 shows a comparison of symptoms between non-ICU and ICU patients. The most significant difference in symptoms between the two groups was dyspnea (P< 0.001).

Table 2. The reported symptoms of pregnant women with COVID-19

Symptom	ICU admission		P-Value
	Yes (N/%)	No (N/%)	
Fever	68.104 (65.4%)	142.296 (48.0%)	0.00
Myalgia	43.97 (44.3%)	123.298 (41.3%)	0.59
Cough	76.101 (75.2%)	179.305 (58.7%)	0.00
Dyspnea	96.105 (91.4%)	222.317 (70.0%)	0.00
Sore throat	16/92 (17.4%)	32.268 (11.9%)	0.18
Nausea	9.92 (9.8%)	33.272 (12.1%)	0.54
Vomiting	4.91 (4.4%)	25.267 (9.4%)	0.13
Diarrhea	3.91 (3.3%)	14.268 (5.2%)	0.57
Loss of appetite	4.90 (4.4%)	12.273 (4.4%)	1.00
Chest pain	7.92 (7.6%)	12.268 (4.5%)	0.28
Abdominal pain	0.90 (0.0%)	12.269 (4.5%)	0.04
Chills	29.93 (31.2%)	57.281 (23.0%)	0.03
Headache	16.92 (17.4%)	40.272 (14.7%)	0.53
Rhinorrhea and nasal congestion	2.90 (2.2%)	9.267 (3.4%)	0.73
Flank pain	2.89 (2.2%)	5.266 (1.9%)	1.00

*The denominator of the fractions is different from the main sample size of each group since the unanswered values are different from each variable

This highlights the severe respiratory distress that ICU patients face and indicates that dyspnea may serve as a noteworthy prognostic indicator for ICU admission. Another prevalent symptom observed in patients in the Intensive Care Unit (ICU) was fever (P= 0.002). This observation suggests that fever may have potential value as an indicator of disease severity and may assist in the identification of patients in need of ICU admission.

It is interesting to note that most symptoms, including fever, cough, sore throat, abdominal pain, and shivering show a significant difference between the two groups.

A mortality rate of 22. 4% was observed among patients who were admitted to ICU. The hospitalization in the ICU represents a significant prognostic factor in determining mortality outcomes. (B=-22.286, P=.000, Table 3).

Table 3. The reported mortality of pregnant women with COVID-19 admitted to the ICU

Variable	Admitted to the ICU		P-Value
	No N= 344 (N/%)	Yes N=116 (N/%)	
Expired	0	26 (22.40%)	B= -22.286
Survived	344 (100.0%)	90 (77.60%)	p-.000

The patients reported a total of sixteen symptoms. In the cohort of patients who expired, dyspnea was observed in the highest percentile of 96.00%. Moreover, a significant proportion of 74.10% of patients exhibiting dyspnea were subsequently discharged from the hospital. The findings of our analysis demonstrated a statistically meaningful distinction between the two groups with regard to dyspnea. The results of logistic regression to correlate with the initial symptoms of patients hospitalized showed that dyspnea is the most important predictor of disease severity (CI=0.70 to 13.540, P<.01). Cough was reported as the second most prevalent symptom in 91.3% of cases among deceased patients, while it was reported in 61.1% of cases among discharged patients. There was a significant difference between the two groups in terms of having a cough as a symptom of illness severity (P-value: 0.002). The results of logistic regression to correlate with the initial symptoms of patients hospitalized showed that Cough is the most important predictor of disease severity (CI=-.48 to 1.56, P<.01). The third most frequently observed initial symptom was fever, reported by 87.0% of the deceased patients and 50.4% of the surviving patients. There existed a significant disparity between the two groups in relation to the presence of fever as an indicator of mortality (P-value: 0.000).

The results of logistic regression to correlate with the initial symptoms of patients hospitalized showed that fever is the most important predictor of disease severity (CI=-.039 to 1.104, P<.01). The least common symptom observed was flank pain, with 5 cases in the non-ICU-admitted patients and 2 cases in the ICU admitted. No observed significant difference between the two groups (P-value: 0.43). Among the symptoms reported by the patients, in addition to dyspnea and cough, three manifested with greater frequency among the patients admitted to the intensive care unit (ICU): fever (P= 0.000), abdominal pain (P-value:0.04), and chills (P= 0.03).

Table 4. The reported symptoms of pregnant women with COVID-19

Symptom	Mortality		P-value	B	95% CI. for EXP(B)	
	Yes N=26 (N/%)	No N= 434 (N/%)			Lower	Upper
Fever	20 (87.0%)	190 (50.4%)	0.000	-1.577	.039	1.104
Myalgia	12 (57.1%)	154 (41.2%)	0.113	-.489	.143	2.623
Cough	21 (91.3%)	234 (61.1%)	0.002	-1.267	.048	1.656
Dyspnea	24 (96.0%)	294 (74.1%)	0.014	-0.024	0.070	13.540
Sore throat	4 (20.0%)	44 (12.9%)	0.268	0.015	0.199	5.173
Nausea	1 (5.0%)	44 (12.9%)	0.303	15.793	0.000	
Vomiting	1 (5.3%)	28 (8.3%)	0.641	16.970	0.000	
Diarrhea	0 (0%)	17 (5.0%)	00.388	19.065	0.000	
Loss of appetite	0 (0%)	16 (4.7%)	.415	-0.025	0.000	
Chest pain	2 (10.0%)	17 (5.0%)	0.285	-0.632	0.020	13.958
Abdominal pain	0 (0.0%)	12 (3.5%)	0.405	-9.617	0.000	
Chills	8 (40.0%)	78 (22.0%)	0.063	0.290	0.319	5.598
Headache	0 (0%)	56 (16.2%)	0.056	18.966	0.000	
Flank pain	1 (5.3%)	6 (1.8%)	0.289	-1.177	0.000	

In our study, a mortality rate of 5. 7% was observed, with a total of 26 cases. The detailed presentation of symptoms reported by the patients is provided in Table 4.

Discussion

The study aims to assess symptoms, critical illness, mortality, and coronavirus disease in obstetric patients. We examined the symptoms of pregnant women with COVID-19 based on the disease severity in the present study. The number of cases of COVID-19 infection has exceeded 610 million worldwide and more than 6.5 million deaths have been reported to date. There needs to be more investigation to determine the effects of the global pandemic on women, fetuses, and obstetric outcomes as the virus spreads throughout the world. In the majority of studies examining the relationship between COVID-19 and pregnancy, it is commonly observed that pregnant individuals are typically in the second or third trimester of their gestation (20-21). According to a prospective cohort study using the UKOSS (UK Obstetric Surveillance System), most women are admitted to hospitals during the third trimester (20). Based on the analysis of 460 patients, it was revealed that the presence of fever, cough, dyspnea, abdominal pain, and shivering during the initial stages of hospitalization poses a greater risk to patients. Moreover, fever, cough, and dyspnea were identified as crucial predictor symptoms for ICU admission, exhibiting a higher mortality rate. Oxygen therapy was administered to several women suffering from respiratory distress.

This study showed that dyspnea was the most common symptom, followed by cough and fever. This finding is consistent with the study of Muhidin et al. (2020) that resulted, among pregnant women with COVID-19, fever and cough were the most common symptoms (22). Furthermore, a cohort study using the United Kingdom Obstetric Surveillance System (UKOSS) found that fever and cough are the most common findings (20). Additionally, studies performed in the early stages of the outbreak indicated the same results. Chen et.al (2020), reported that cough and fever were prevalent symptoms observed in pregnant women affected by COVID-19. In contrast to the findings of the present study, their findings indicated

that shortness of breath was observed less frequently (22). On the other hand, according to a study by Smith et al. (2020), a majority of the participants were asymptomatic (24).

In the present study, we evaluated the prognostic value of clinical symptoms among pregnant women with COVID-19. According to our analysis, patients who experienced dyspnea, fever, cough, abdominal pain, or chills were more likely to be admitted to the intensive care unit. In 2020, Valeria et al. conducted a similar study; they found that the clinical symptoms associated with severe disease were dyspnea and fever, that consistent with our research but still not support our findings on the significance of the three other symptoms (25). Furthermore, a retrospective study conducted by Xinkui et al. (2020) on non-pregnant patients has shown that dyspnea is the only symptom that indicates a severe disease (26). Also, according to Huang et al. (2020), fever and dyspnea, differed significantly among patients with mild and severe disease, further illustrating the discrepancy in the literature (27). Numerous studies have consistently identified dyspnea as a detrimental symptom among both pregnant and non-pregnant patients with COVID-19.

The rate of maternal mortality was 5.7% in our study which is notably higher than the reported rates of 1% in the United Kingdom (20), 0. 2% in the United States (28), and 1. 5% in Mexico (16). Nevertheless, the nationwide population-based cohort study conducted in Brazil has determined that the incidence of maternal mortality in hospitals increased to 12. 5% of this finding exceeds the rate observed in our own study (15). It appears that a multitude of factors contribute to these outcomes, including the economic conditions of nations, availability of the vaccine, and comorbidities among the individuals. It is evident that high-income countries equipped with efficiently structured obstetric care services exhibited markedly lower rates of maternal mortality resulting from COVID-19 in comparison to low-income nations. In our country global sanctions have further exacerbated the situation.

Our study possesses a distinct advantage in comparison to prior studies as we examined a considerably larger study population. This attribute contributes to enhancing the reliability

of the obtained results. Additionally, the utilization of PCR and HRCT investigations to verify COVID-19 infection provides enhanced support to the outcomes. The retrospective nature of this study is one of its limitations.

Furthermore, our study did not conduct postpartum patient follow-ups to investigate additional issues such as maternal mortality within 42 days of childbirth or neonatal outcomes, which could be the focus of the future research.

Although the findings may not be generalizable, they provide a basis for further research to identify the key symptoms indicative of a negative prognosis among these patients and initiate treatment as soon as possible.

Conclusion

This study found that pregnant women who experienced fever, dyspnea, cough, chills, or abdominal pain were more likely to develop severe disease. Prompt and expeditious diagnosis should be initiated in pregnant women with COVID-19 infection, as timely intervention plays a critical role in the management of this condition. Understanding the manifestations of COVID-19 and the correlation between these manifestations and the disease heightened morbidity will facilitate the effective management of this condition in pregnant women by the healthcare team.

Declarations

Acknowledgments

Conflicts of interest

The authors declared no conflicts of interest.

Ethical Considerations

The Ethics Committee of Mashhad University of Medical Sciences approved the present study by the ethical code of IR.MUMS.REC.1399.214.

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Authors' contribution

M.M and M.M contributed substantially in the conception and design of the study. F.Z and N.J carried out the data collection. J.J and T.S analyzed and interpreted the data. A.M drafted the manuscript. M.M reviewed the manuscript critically for important intellectual content. All authors read and approved the final manuscript and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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