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Clinical Manifestation, Laboratory Findings and Adverse Outcomes of COVID 19 Infection in Pregnant Women: A Cross-Sectional Study in the West of Iran

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ABSTRACT

Background & Objective: Pregnancy is a unique immunological condition in which the immune system is affected and therefore there is a greater risk of severe disease and mortality from COVID-19 disease. The present study aimed to evaluate the clinical manifestation, laboratory findings, and adverse outcomes among a population of pregnant women confirmed with COVID 19 infection.

Materials & Methods: In present cross-sectional study, all pregnant women with COVID-19 referred to Mousavi Hospital in Zanjan City from February 2020 to August 2021 including 232 patients were examined. We used a researcher-made checklist to extract the required information, including socio-demographic data, potential risk factors, clinical manifestations, laboratory parameters, and fetal, and neonatal outcomes of the patients. Comparison of laboratory parameters in women with COVID-19 according to ICU admission was made using independent t-test and Mann-Whitney U test.

Results: 47.4%, of women were 30 to 40 years old, 45.7% were illiterate. Weakness, myalgia, dry cough, and fatigue were the most common clinical symptoms (>90%). Patients had abnormal levels of ALT and AST, whereas the means of other laboratory parameters were in the normal range. Forty- one (17.6%) of patients were admitted to the ICU. The means of C - reactive protein (46.58 vs. 25.87), lactate dehydrogenase (586.31 vs. 480.97), Blood urea nitrogen (9.43 vs. 8.26), and erythrocyte sedimentation rate (62.40 vs. 46.11) were statistically higher in patients admitted to ICU than those who were not in the ICU (P <0.05). Mortality rates among women who had a vaginal delivery and C-section were 3% and 6.1%, respectively.

Conclusion: The most common laboratory findings in COVID-19- infected mothers were lymphopenia and elevated CRP, ALT, D-Dimer, and LDH. An increased hospitalization in ICU and higher rates of mother and fetal death were complications of pregnancy and childbirth in COVID-19- infected women.

Keywords: Risk factor, COVID-19, Pregnancy, Maternal death

Introduction

Novel coronavirus disease 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) led to 243,006,693 confirmed cases and 4,937,199 confirmed deaths through October 2021 (1). One of the particularly vulnerable populations to COVID 19 infection is pregnant women. They are susceptible to viral infections e.g. COVID 19 due to physiological changes and immunosuppressive conditions during pregnancy (2). Although the results of studies are mainly in favor of mild or asymptomatic disease due to COVID-19 infection in pregnant women (3-5), the risk of adverse pregnancy outcomes such as preterm birth, cesarean delivery, and admission to the intensive care unit (ICU) among pregnant women with COVID 19 may still be higher than non-pregnant women (6).

Previous studies have shown that COVID 19 infection can lead to significant changes in laboratory indicators such as platelet count, white blood cells, lymphocyte count, hemoglobin, C - reactive protein, creatinine, alanine aminotransferase, aspartate aminotransferase, D-Dimer, lactate dehydrogenase, blood urea nitrogen, erythrocyte sedimentation rate, and ferritin (7-9). Most of these studies focus on the evaluation of laboratory indicators in the general population and there is scant research on pregnant women (10). However, more evidence is still needed on the status of these indicators in pregnant women to guide clinical decision-making. Another issue that needs further investigation is the clinical manifestations of pregnant women with COVID-19 because detailed clinical manifestations and associations between clinical features and adverse

outcomes in pregnant women are sparse (11). Apart from the clinical symptoms and laboratory indicators, the type of used treatment for COVID-19 in pregnant women is another challenge because the randomized controlled trials do not include pregnant women and the safety and efficacy of available treatments for pregnant women with COVID-19 in such a population are still controversial (12). Status of clinical symptoms, laboratory findings, treatment and management, and adverse outcomes of COVID-19 infection in pregnant women require further detailed investigation, so the present study aimed to evaluate and describe the aforementioned characteristics among pregnant women with confirmed COVID 19 infection.

Materials and Methods

In the present retrospective cross-sectional study, all COVID-19 positive pregnant women referred to Mousavi Hospital in Zanjan City from February 2020 to August 2021 including 232 patients were investigated by census method.

The Ethics Committee of Zanjan University of Medical Sciences approved the study (Ethic committee code: IR.ZUMS.REC.1400.303). In this study only pregnant women with positive real time reverse transcriptase polymerase chain reaction (RT-PCR) on samples from upper respiratory nasopharyngeal swabs regardless of disease severity were considered as inclusion criteria and were assessed. Patients with clinical or radiological symptoms consistent with COVID -19 who had negative PCR tests were excluded from the study. Moreover, patients with incomplete medical records or unknown medical outcome were excluded.

We used a researcher-made checklist to extract the required information, including socio-demographic data and risk factors of patients (the patient's age, history of underlying disease, gestational age, education, location, BMI, contact with COVID-19 cases, history of travel), clinical manifestations of the patients, laboratory parameters including platelet count, white blood cells, lymphocyte count, hemoglobin, C-Reactive protein, creatinine, alanine aminotransferase, aspartate aminotransferase, D-Dimer, lactate dehydrogenase, blood urea nitrogen, erythrocyte sedimentation rate, ferritin, prothrombin time and activated partial thromboplastin time, and fetal, and neonatal outcomes of the pregnancy including hospital duration, delivery type, Apgar score in the first and fifth minutes, and death. The information was extracted from hospital's archive system and patient files by trained midwives. Descriptive statistics including mean and standard deviation were used for describing the continuous variables and frequency and percentage were utilized for describing the categorical variables. We arranged our findings in frequency tables and charts. Comparison of laboratory parameters in women with COVID-19 according to ICU admission was made using independent t-Test and Mann-Whitney U test. Data were analyzed using Stata 14 (StataCorp, College Station, TX, USA).

Results

Socio-demographic characteristics, risk factors and pregnancy history of pregnant women with COVID-19 among the study population are shown in Table1. A large number of women were 30 to 40 years old (47.4%), illiterate (45.7%) and from Zanjan City (55.2%). Nearly 90% of women reported close contact with COVID-19 cases. None of them reported any previous COVID-19 infection. The majority of women had 1 or 2 gravidities , and 62.9% had LMP more than 28 weeks.

Table 1. Sociodemographic characteristics, risk factors and pregnancy history of pregnant women with COVID-19 (n=232)

Characteristics	N (%)
Age (year)	
=<30	109 (47)
30-40	110 (47.4)
>40	13 (5.6)
Education	
Illiterate	106 (45.7)
High school diploma	90 (38.8)
University degree	36 (15.5)
Location	
Village	116 (50)
City	116 (50)
Town	
Zanjan	128 (55.2)

Characteristics	N (%)
Out of Zanjan	104 (44.8)
Body mass index (BMI)	
=<25	123 (53)
25-30	83 (35.8)
>30	26 (11.2)
Contact with COVID-19 cases	
No	24 (10.3)
Yes	208 (89.7)
History of travel	
No	212 (91.4)
Yes	20 (8.6)
Gravidity	
1	60 (25.9)
2	69 (29.7)
3	50 (21.6)
>=4	53 (22.8)
Last delivery	
None	56 (24.1)
Natural vaginal delivery	95 (40.9)
Cesarean delivery	65 (28)
Abortion	16 (6.9)
Last Menstrual Period (weeks)	
<28	68 (29.3)
>=28	150 (64.7)

Rates of disease history and clinical symptoms in pregnant women with COVID-19 are indicated in Figure 1. Hypothyroidism (22.8%), preeclampsia (9.5%), and gestational diabetes (8.6%) were the highest disease history in these patients (Figure 1A). Weakness, myalgia, dry cough and fatigue were the most common clinical symptoms in more than 90% of the patients (Figure 1B).

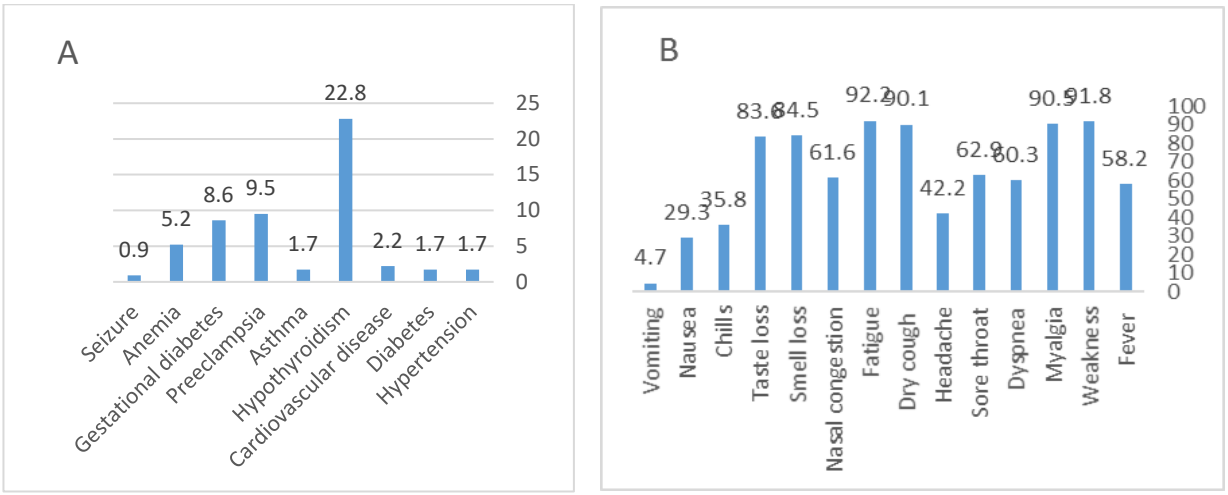

Figure 1. Percent of A) history of disease, B) clinical symptoms in pregnant women with COVID-19

Laboratory parameters in pregnant women with COVID-19 are shown in Table 2. The mean rates (SD) of C-reactive protein, ALT and AST were 29.74 (25.43), 34.90 (38.81) and 43.09 (30.62), respectively. The mean rates of other laboratory parameters fall in normal range.

Table 2. Laboratory parameters in pregnant women with COVID-19

Laboratory parameters	Mean (SD)	Min	Max	Normal Range	Less than lower limit of normal range n (%)	Higher than upper limit of normal range n (%)
Platelet count (10^3/UL)	179.26 (55.86)	26	376	150 to 450	74 (31.9)	-
White blood cells (10^9/Ul)	7.84 (2.90)	3.10	21.80	5 to 13	32 (13.8)	12 (5.2)
Lymphocyte count (%)	16.49 (7.21)	3.70	53.00	20 to 40	172 (74.1)	2 (0.9)
Hemoglobin (g/dl)	12.53 (8.45)	8.30	139.00	10 to 15	16 (6.9)	5 (2.2)
C-Reactive Protein (mg/dl)	29.74 (25.43)	1.00	123.00	0 to 2	-	220 (94.8)
Creatinine (mg/dl)	0.72 (0.14)	0.50	1.50	0.4 to 0.9	-	34 (14.7)
Alanine aminotransferase (U/L)	34.90 (38.81)	5.00	323.00	2 to 25	-	108 (46.6)
Aspartate aminotransferase (U/L)	43.09 (30.62)	10	248	3 to 23	-	107 (46.1)
D-Dimer (ng/mL)	1033.18 (1664.77)	0.1	6926	483 to 2256	47 (20.3)	13 (5.6)
Lactate dehydrogenase (U/L)	500.04 (184.83)	4.70	1545	200 to 400	2 (0.9)	157 (67.7)
Blood urea nitrogen (mg/dL)	8.46 (3.21)	3.00	24.00	5 to 12	33 (14.2)	27 (11.6)
Erythrocyte sedimentation rate (mm/h)	48.92 (24.15)	1.00	120.00	30 to 70	53 (22.8)	46 (19.8)
Ferritin (ng/mL)	128.28 (116.95)	17.00	532.00	2 to 230	-	5 (2.2)
Prothrombin time (seconds)	13.04 (0.66)	10.00	18.00	9.5 to 13.4	-	23 (9.9)
Activated partial thromboplastin time (seconds)	34.34 (4.27)	24.20	52.00	24.2 to 38.1	-	28 (12.1)

41 (17.6%) patients were admitted to the ICU and 23 (52%) were hospitalized for 5 or more days in the ICU. The comparison of laboratory parameters between pregnant women in the ICU and those not hospitalized in the ICU are shown in Table 3. The means of C-Reactive Protein (46.58 vs. 25.87), Lactate dehydrogenase (586.31 vs. 480.97), Blood urea nitrogen (9.43 vs. 8.26) and Erythrocyte sedimentation rate (62.40 vs. 46.11) and D-Dimer (1240.72 vs.452.1) were statistically higher in the patients admitted in the ICU than those not hospitalized in the ICU (P <0.05). Mean of lymphocyte count (12.47 vs. 17.28) was statistically lower in the patients admitted in the ICU than those not hospitalized in the ICU (P <0.05).

Table 3. Comparison of laboratory parameters in women with COVID-19 according to ICU admission

Laboratory parameters	Not hospitalized in ICU	Admitted to ICU	P-value*
Platelet count (10^3/UL)	176.77 (53.99)	188.07 (61.91)	0.23
White blood cells (10^9/Ul)	7.81 (3.1)	8.06 (2.40)	0.61
Lymphocyte count (%)	17.28 (7.25)	12.47 (5.10)	<0.001
Hemoglobin (g/dl)	12.77 (9.30)	11.43 (1.24)	0.36
C-Reactive Protein (mg/dl)	25. 87 (23.67)	46.58 (26.03)	<0.001
Creatinine (mg/dl)	0.72 (0.13)	0.75 (0.17)	0.16
Alanine aminotransferase (U/L)	64.10 (46.46)	60.54 (49.10)	0.77
Aspartate aminotransferase (U/L)	77.85 (66.54)	80.08 (53.28)	0.86
D-Dimer (ng/mL)	1240.72 (1677.28)	452.11 (1088.51)	0.04**
Lactate dehydrogenase (U/L)	480.97 (181.61)	586.31 (178.61)	0.001
Blood urea nitrogen (mg/dL)	8.26 (2.84)	9.43 (4.50)	0.03
Erythrocyte sedimentation rate (mm/h)	46.11 (22.85)	62.40 (26.15)	<0.001
Ferritin (ng/mL)	92.34 (66.17)	156.73 (139.88)	0.11
Prothrombin time (seconds)	13.03 (0.66)	13.11 (0.69)	0.46
Activated partial thromboplastin time (seconds)	34.21 (4.17)	35.06 (4.71)	0.25

* according to independent t-test
** according to Mann-Whitney U test

The pregnancy outcomes among women after vaginal delivery and cesarean-section are shown in Table 4. Mortality rates among women who had vaginal delivery and cesarean-section were 3% and 6.1%, respectively. The number of fetal death among women with cesarean section was 5 (10.2%), whereas no fetal death was found among women with vaginal delivery. The rate of NICU admission among women with cesarean-section was higher than those with vaginal delivery (89.6% vs. 71.4%). More than 85% of women with vaginal delivery had 1 minute Apgar score of 9, while women with cesarean section 63.3% had 1 minute Apgar score of 9. The number of fetal weights of lower than 2500 gr among women with vaginal delivery and C-section were 2 (7.1%) and 13 (27.1%), respectively. Our results showed that the number of premature birth was higher in women with cesarean-section than women with vaginal delivery (0 vs. 18.4%, P=0.016).

Table 4. Pregnancy outcomes among pregnant women with COVID 19 after vaginal delivery and cesarean section

	Vaginal delivery	Cesarean section
Death		
Mother	1 (3%)	3 (6.1%)
Fetal	-	5 (10.2%)
NICU admission		
No	8 (28.6%)	5 (10.4%)
Yes	20 (71.4%)	43 (89.6%)
Apgar score (first minute)		
0	0	1 (2%)
3	1 (3.6%)	2 (4.1%)
4	0	1 (2%)

	Vaginal delivery	Cesarean section
6	0	2 (4.1%)
7	2 (7.1%)	1 (2%)
8	1 (3.6%)	11 (22.4%)
9	24 (85.7%)	31 (63.3%)
Apgar score (fifth minute)		
0	0	1 (2%)
5	0	1 (2%)
8	0	4 (8.2%)
9	3 (10.7%)	9 (18.4%)
10	25 (89.3%)	34 (69.4%)
Fetal weight		
<2500 gr	2 (7.1%)	13 (27.1%)
>=2500 gr	26 (92.9%)	35 (72.9%)

Discussion

This study was conducted in order to investigate the risk factors, clinical and laboratory findings and adverse outcomes of COVID 19 infection in pregnant women during the two years after initiation of COVID-19 pandemic in Zanjan. The main findings of this study were as follows: in more than 90% of the patients weakness, myalgia, dry cough and fatigue were the most common clinical symptoms. Approximately 20% of the women were admitted to ICU. COVID-19 was responsible for the termination of pregnancy in 5.6% of pregnant women. 2.2% of mothers and neonates died due to COVID-19 infection. Regarding laboratory parameters, nearly 75% of the women had lymphocyte count lower than normal range and 95% had CRP higher than normal range. ALT and LDH were the other two elevated parameters in these patients. The mean rates of CRP, LDH, BUN, D-Dimer and ESR were statistically higher in the patients admitted in the ICU, while lymphocyte count was statistically lower in these patients.

According to CDC report most common symptoms of COVID-19 in general population were cough (84%), fever (80%), myalgia (63%), chills (63%) and fatigue (62%) (13). Although this disease is more asymptomatic in pregnant women than in general population due to early screening for pregnant patients (14), in the present study, symptomatic cases who were hospitalized were investigated and weakness, myalgia, dry cough and fatigue were common in patients.

In line with the current study, Chen et al., found that COVID-19 -infected pregnant women had enhanced innate immune response evident by elevated neutrophils and CRP (15). In another study by Vakili et al., consistent with our findings, high level of CRP was common in the COVID-19- infected pregnant women (16). Moreover, in the conducted study by Sahin et al., Neutrophil lymphocyte ratio and CRP, were significantly higher in severe COVID-19 cases than in mild or moderate cases (17). Moreover, the higher level of CRP in pregnant women was obtained in the Wei et al., study (18). It is inferred that these findings are typical of pregnancy and related to adaptations to gestation.

It has been reported that pregnant women with COVID-19 had significantly higher TBil level as a biomarkers for liver disease (19). In the conducted study by Guan et al., 21.3% of patients had ALT elevation (20). Moreover, Zhang et al., reported that 14–53% of pregnant women infected with COVID-19, had abnormal levels of AST and ALT (21). In our study consistent with this result, 46% of patients had elevated ALT. It seems that COVID-19 could affect the liver function of pregnant women. Results of the meta-analysis in this regard which showed that pregnant patients had similar changes of laboratory values such as altered leucocyte and platelet counts (increased or decreased), elevated levels of CRP, and D-Dimer are in line with our finding (22). Can et al, concluded that COVID-19 may cause liver injury and abnormal LFTs in these patients can be due to prolonged hospital stay. Moreover, the administration of antiviral drugs is the risk factor for liver injury during hospitalization and therefore, COVID-19 -positive pregnant women should be monitored for evaluating LFTs (23).

In this study, approximately one-fifth of patients were hospitalized in ICU. The higher death rates and need for ICU admission in COVID-19- infected

pregnant women have been shown in previous studies (24, 25). Martinez-Portilla et al., revealed that pregnant women had 1.84% increased odds for death, 1.86% for pneumonia and ICU admission compared to non-pregnant women (26). The association between higher CRP level at the first admission and need for ICU admission have been shown in Tunc et al., study (27). Physiological respiratory changes and attenuation of the immune system cause pregnant women to be at a higher risk of severe adverse outcomes. During the pregnancy due to physiological changes, oxygen use increases by 21%. Moreover, progesterone changes the nasal mucosa and consequently facilitates the retention of the virus in the upper respiratory tract, thus making it difficult for the host immunity to remove it. Therefore, these physiological changes increase the need for ICU hospitalization in pregnant women (28).

However, this study had some limitations. First, 64% of the women were in postpartum period, therefore, the outcome regarding delivery and neonates' health were unknown. Second, due to the retrospective nature of the study, we could not assess long-term side-effects of the infection on mothers and neonates. Third, this study was conducted on hospitalized pregnant women, therefore, the results could not be generalizable to the total pregnant women. Finally, lack of the control group among pregnant women without COVID-19 infection to compare the studied variables between the two groups was another limitation of this study. However, conducting the study in the long time period and assessing many of clinical and laboratory parameters in these patients can be considered as the strengths of the study.

Conclusion

According to findings of the study, it can be concluded that the clinical symptoms in pregnant women with COVID-19 are similar to non-pregnant women. The most common laboratory findings in infected mothers were lymphopenia and elevated CRP, ALT and LDH. An increased hospitalization in ICU and higher rates of mother and fetal death were the complications of pregnancy and childbirth in COVID-19 -infected women.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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