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Comparison of the pregnant and non-pregnant women of reproductive age hospitalized due to COVID-19 infection

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Abstract

COVID-19 affects pregnant women more severely than nonpregnant women of reproductive age. However, the rate of critical illness and fatality reported in other studies varied in a wide range in both groups. The study aims to investigate the clinical outcomes of COVID-19 in the pregnant and nonpregnant matched control patients admitted to the hospital. Pregnant and nonpregnant patients of reproductive age (18-45 years) infected with COVID-19 who were admitted to Ondokuz Mayıs University Hospital, Samsun, Turkey, from March 11 to December 11, 2020, were enrolled in the study. The clinical, radiological, and laboratory data of the patients were analyzed retrospectively. A total of 153 patients were investigated; 123 were nonpregnant, and 30 were pregnant. Emergency delivery occurred in 5 (17%) pregnant women due to acute respiratory failure associated with COVID-19 and 1 (3%) pregnant woman due to obstetric reasons. Four premature births, one perinatal death, and no stillbirth or miscarriage were reported. The rate of admission to the intensive care unit (ICU) [7/30 (23.3%) vs 3/123 (2.4%), p<0.001] and the need for invasive mechanical ventilation (IMV) [5/30 (17.0%) vs 2/123 (1.6%), p=0.003] were significantly higher in pregnant than in non-pregnant patients. However, hospital length of stay (HLOS) and mortality did not differ between groups: HLOS was median 4 vs 5 days, p=0.68, and the mortality rate was 1/123 (0.8%) vs 0/30 (0%), p=0.62 in nonpregnant and pregnant patients respectively. We observed that COVID-19 has a more severe course in pregnant women versus the nonpregnant control group, but no difference was noted in terms of hospital length of stay and mortality. The overall case fatality rate of COVID-19 in hospitalized pregnant or nonpregnant women of reproductive age was found to be much lower than the general hospitalized population worldwide.

Keywords: COVID-19 infection, pregnancy, nonpregnant patient, mortality, critical illness

1. Introduction

Coronavirus disease of 2019 (COVID-19) caused by novel coronavirus SARS-CoV-2 may be asymptomatic or symptomatic in pregnant women. While more than 90% of pregnant women infected with SARS-CoV-2 may recover without hospitalization, the rest may develop rapid clinical worsening, and symptomatic pregnant women are at higher risk for severe illness and death compared to nonpregnant women of reproductive age (1-5). Current evidence suggests that pregnancy does not increase susceptibility to COVID-19 compared to young nonpregnant women but does increase the severity of illness, including increased need for intensive care and mechanical ventilators or respiratory support and an increased risk of death (1, 6-14). In addition, pregnant patients with COVID-19 may be at higher risk of preterm birth compared to uninfected pregnant women. However, COVID-19 does not seem to increase the risk of miscarriage or congenital anomalies, and neonatal outcomes appear to be good. Physiological changes during pregnancy, such as decreased functional residual capacity, diaphragm elevation, edema in the respiratory mucosa, and impaired cellular immunity, may cause the viral disease to be more severe as they make them susceptible to viral infection and hypoxia (15). Another possible explanation may be the overexpression of ACE2 receptors in pregnancy compared to nonpregnant; the uterus and placenta are the main sources (16). Since the ACE2 receptor serves as a binding site for SARS-CoV-2, after the viral invasion, the ACE2 receptor is down-regulated, decreasing the metabolism of angiotensin II. Elevated levels of

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angiotensin II promote vasoconstriction, inflammation, and a procoagulopathic environment that occurs in COVID-19 (17). However, some data do not support an increased risk of severe COVID-19 or mortality in pregnancy compared with nonpregnant female patients of reproductive age (18-20). Consequently, despite information about the virus and COVID-19 continues to accrue, the effects of COVID-19 infection on pregnancy are not entirely resolved. In this comparative study, we report the clinical features of the pregnant and nonpregnant women of reproductive age admitted to the hospital with confirmed COVID-19 infection.

2. Materials and Methods

2.1. Study design

Pregnant and nonpregnant women of reproductive age (18-45 years) who were admitted to the hospital with the diagnosis of COVID-19 between March 11 2020 and December 11, 2020, were included in the study. We retrospectively reviewed the patients' clinical, radiological, and laboratory data through their electronic files. Since the onset of the pandemic, our hospital has been serving as a reference university hospital, particularly for severe or critical COVID-19 pregnant women. Exclusion criteria were defined as age below 18 or above 45 years, patients hospitalized with high clinical suspicion of COVID-19 but whose polymerase chain reaction (PCR) was detected negative, and who had no typical findings on chest computed tomography (CT) as well as no history of close exposure, preoperative patients who had been routinely tested for COVID-19 PCR but had a negative result, and patients with advanced cancer at terminal stage.

2.2. Diagnosis and severity of illness

The diagnosis of COVID-19 was confirmed by a PCR positivity specimen obtained from a nasopharyngeal swab. For patients with PCR negative, either antibody positivity alone or a combination of household contact history and typical findings on chest CT were considered sufficient to confirm COVID-19 diagnosis. Typical chest CT findings of COVID-19 were accepted as ground-glass opacities, crazy paving patterns, and/or consolidation. The severity of the illness was categorized into three groups based on the clinical spectrum of SARS-CoV-2 infection defined by the National Institute of Health (21). Asymptomatic to mild infection covers patients with no sign or symptom to any symptom or sign except shortness of breath, dyspnea, or abnormal chest imaging.

Moderate infection refers to patients with any sign or symptom of lower respiratory disease on clinical assessment or imaging as well as oxygen saturation (SpO2) ≥94 on ambient air at sea level.

Severe to critical infections include patients with SpO2 <94% on room air at sea level, respiratory rate >30 breaths/min, PaO2/FiO2<300, lung infiltrates >50%, respiratory failure requiring oxygen therapy and/or respiratory support, septic shock and /or multiorgan failure. Pulmonary involvement was assessed only in patients who were undertaken chest CT.

Supplemental oxygen and respiratory support were given algorithmically according to the oxygen need in the following order as appropriate; nasal cannula, simple face mask, reservoir bag, high flow nasal cannula (HFNC), noninvasive mechanical ventilation (NIV), invasive mechanical ventilation (IMV). Patients with septic shock and multiorgan failure were triaged according to The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis 3) (22).

2.3. Scanning protocol

Chest CT was performed with a multidetector scanner (Aquillon Prime SP, Toshiba Medical Systems Corporation, Japan) using the following parameters: 72 kW generator, 0.35 second rotation time, 78 cm gantry bore, and automatic tube current modulation. The CT scans were obtained with the patient placed in the supine position at the end inspiring period without using contrast media. Images were acquired and reconstructed as axial sections with 1 mm thickness and dose reduction protocol. The scans were interpreted and reported by ME, a thoracic radiologist with 20 years of experience. Informed consent had been obtained from all pregnant patients before CT scanning.

2.4. Assessment of pulmonary involvement in CT

The severity level of COVID-19 disease according to the radiological involvement on CT was determined based on a semi-quantitative scoring system (23). A visual score between 0 and 5 was given to the percentage of the area of radiological involvement for each lung lobe. The scoring was as follows: 0 points for no involvement, 1 point for <5% involvement, 2 points for 5-25% involvement, 3 points for 26-49% involvement, 4 points for 50-75 % involvement, and 5 points for >75% involvement. The total score obtained by summing the points calculated for 5 lobes, including the upper, middle, and lower lobes of the right lung and the upper and lower lobes of the left lung, was defined as the CT severity score (CT-SS). The CT-SS of each patient was qualitatively classified as mild (score 1-5), moderate (score 6-14), or severe (15-25) (24). Examples of scoring some CT sections are given in Fig. 1.

2.5. Statistical analysis

The data were analyzed with the SPSS program, version 21.0. Categorical parameters were expressed as percentage and frequency. Continuous data were expressed as mean with standard deviation (SD) and as median with interquartile range (IQR) for normal and non-normal distributed data, respectively. Comparison between categorical variables was made using the X2 test or Fisher's exact test. Continuous variables were compared with each other using parametric test Student T or nonparametric test Mann Whitney U, where appropriate. P values less than 0.05 were considered statistically significant.

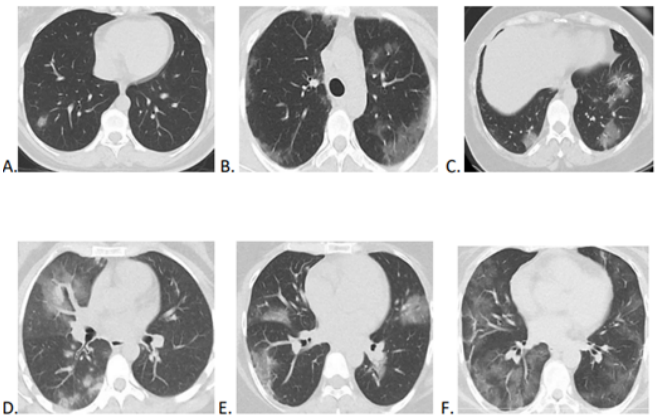

Fig. 1. Examples of CT-SS calculated on CT sections of some patients. A) CT-SS is 1 points; for area of radiologic involvement <5% in the right lung. B) CT-SS is 4 points; 2 points for radiologic involvement of 5-25% in each lung. C) CT-SS is 4 points; 1 points for area of radiologic involvement <5% in the right lung and 3 points for radiologic involvement of 26-49% in the left lung. D) CT-SS is 5 points; 4 points for radiologic involvement of 50-75% in the right lung and 1 point for radiologic involvement in the left lung. E) CT-SS is 5 points; 3 points for radiologic involvement of 26-49% in the right lung and 2 points for radiologic involvement of 5-25% in the left lung. F) CT-SS is 10 points; 5 points for radiologic involvement >75% in each lung. CT-SS: computed tomography severity score

3. Results

A total of 284 patients were screened, and 153 met the inclusion criteria. All the 30 pregnant patients tested positive for PCR, and 15 of 123 nonpregnant patients tested negative for PCR. The demographic and clinical characteristics of the patients are listed in table 1. The mean age was higher in the nonpregnant group compared to pregnant women; 32.8 (7.5) vs 30.1 (5.4) years, p=0.03. Pregnant patients were admitted at a median of 33.5 (26.8-38.0) weeks, half of them delivered during the hospital stay. Of the 15 deliveries, six were performed with the urgent cesarean section, five of which were due to respiratory distress, and one was due to an obstetric problem. Four preterm births (PTB) were recorded in the study, 3 out of 4 were<34 weeks, and 1 out of 4 was <37 weeks of pregnancy. Among newborns, only one baby born at 26 weeks of gestation died.

The rate of asymptomatic patients was higher among pregnant women, though not statistically significant; 10% (3/30) vs 3.2% (4/123), p=0.37. The cough was the most common symptom in all patients. Other symptoms, including muscle or body aches, headache, fever or chills, and diarrhea were significantly more frequent in nonpregnant than in pregnant patients. Asthma was the most common pre-existing condition, with a similar proportion of nonpregnant and pregnant patients being 8.1% (10/123) and 6.7% (2/30), respectively. Autoimmune disease (9/123 vs 1/30), diabetes (5/123 vs 1/30), and solid organ transplant (4/123 vs 1/30) were more common in nonpregnant women compared to pregnant women. History of active smoking (9/123), hypertension (3/123), and obesity (3/123) were recorded only among nonpregnant women.

CT was performed on 126 patients. Pulmonary involvement was detected in 83 of them. The CT-SS of 80 patients could be calculated as three CTs were reported as indeterminately. Semi-quantitative SS-CT was a median of 2 (0-6) points for the nonpregnant group, while 9 (0.8-17.3) points for the pregnant group (p=0.022). CT-SS was compatible with severe disease in 4.2% of nonpregnant patients and 44.0% of pregnant women.

Patient distribution rates between groups were significantly different according to disease severity (p=0.004). Patients with asymptomatic or mild illness were 35% (43/123) vs 56% (17/30), moderate illness was 50% (62/123) vs 16% (5/30), and severe or critical illness was 15% (18/123) vs 26% (8/30) in nonpregnant and pregnant cases respectively. There was no difference in terms of oxygen requirement (non-pregnant, 17.1 % vs pregnant, 30.0%; p=0.11). However, the need for intensive care and IMV was significantly higher in pregnant patients than in nonpregnant patients at 23.3% (7/30) and 17% (5/30) versus 2.4% (3/123) and 1.6% (2/123), respectively (p<0.001 and p=0.003).

Among the patients admitted to the ICU, 3 out of 7 pregnant women were referred from other hospitals, but none of the nonpregnant patients had a referral history. Of the 153 patients, only 10 (6.5%) were admitted to ICU, and one patient among them died who was a nonpregnant case with restrictive lung disease due to scoliosis. Thus, the overall case fatality rate corresponded to 0.7% (1/153) in the study population. The length of hospital stay was similar in both groups: median 4 days (2.5-7.0) and 5 days (2.0-10.0) for nonpregnant and pregnant patients, respectively (Table 1).

A comparison of laboratory parameters is summarized in table 2. Inflammation markers and D-dimer levels were found to be significantly elevated in the pregnant group. Median values for C-reactive protein (CRP) was 40.5 vs 6.4 mg/L (p<0.001), erythrocyte sedimentation rate (ESR) was 64.0 vs 24.0 mm/h (p=0.001) and D-dimer was 1070.5 vs 289.0 ng/mL (p<0.001) in pregnant and non-pregnant patients respectively. While lymphocyte (L) count was lower (0.9 vs 1.2 x103/uL; p=0.039), neutrophil (N) and neutrophil-lymphocyte ratio (NLR) was higher (5.9 vs 3.2x103/uL; p<0.001 and 5.8 vs 2.3; p<0.001 respectively) in pregnant compared to non-pregnant population. Hemoglobin (Hb), procalcitonin (ProCT), prothrombin time (PT), alkaline phosphatase (ALP), and total bilirubin showed a statistically significant difference between the groups but are of uncertain clinical significance.

Characteristics of critically ill patients are given in table 3. The median age was 33 years, with IQR of 26.8 and 36. Of these patients, only three had a pre-existing disease, two had obesity and one had scoliosis, and all were nonpregnant. Laboratory parameters were markedly different from the study population. The median values for L were 0.65 vs

1.20x103/uL, NLR was 9.60 vs 2.90, CRP was 162.5 vs 9.9 mg/L, and D-Dimer was 1039.5 vs 391 ng/mL, and ferritin was 212 vs 48.3 ng/mL in critical and overall patients respectively. CT-SS of the critical patients was higher than the overall value median of 13.5 vs 2.0 points. Nine out of ten patients were admitted with acute respiratory distress syndrome (ARDS) having moderate to severe lung involvement on chest CT. One patient was admitted for postoperative respiratory failure and underwent cesarean delivery. Sequential organ failure assessment (SOFA) score and PaO2/FiO2 at ICU admission were median of 2.5 points (2.0-4.8) and 143.5 mmHg (117.8-167.0), respectively. Of 10 patients admitted to ICU, one patient recovered with a reservoir bag, two patients with HFNC, and seven patients with IMV. Two patients developed septic shock, and one of them died. Length of stay in ICU (LOS-ICU) was median 9 days (7.0-28.0).

Table 1. Demographic and clinical characteristics of the study population

Variables	All patients N=153	Nonpregnants N=123	Pregnants N=30	P value
Age, mean (SD)	32.3 (7.2)	32.8 (7.5)	30.1 (5.4)	**0.029**
Pregnancy week, median (IQR)			33.5(26.8-38.0)	NA
Delivery during hospital stay, N (%)			15(50)	NA
Urgent delivery, N (%)			6 (40)	NA
Preterm birth, N (%)			4 (26)	NA
Perinatal death, N (%)			1(7)	NA
Presence of symptom, (N%)				0.137
Yes	7 (4.5)	4 (3.2)	3 (10.0)	
No	146 (95.5)	119 (96.8)	27 (90.0)	
Symptom, N (%)				
Cough	96 (62.7)	78 (63.4)	18 (60)	0.729
Muscle or body aches	75 (49)	67 (54.5)	8 (26.7)	**0.006**
Fatigue	74 (48.4)	63 (51.2)	11 (36.7)	0.153
Headache	68 (44.4)	61 (49.6)	7 (23.3)	**0.009**
Shortness of breath	61 (39.9)	51 (41.5)	10 (33.3)	0.415
Fever or chills	55 (35.9)	50 (40.7)	5 (16.7)	**0.014**
Sore throat	54 (35.3)	47 (38.2)	7 (23.3)	0.126
New loss of state or smell	35 (22.9)	31 (25.2)	4 (13.3)	0.159
Chest pain	30 (19.6)	26 (21.1)	4 (13.3)	0.334
Diarrhea	26 (17)	25 (20.3)	1 (3.3)	**0.026**
Runny nose	18 (11.8)	12 (9.8)	6 (20.0)	0.125
PCR, N (%)				NA
Positive	138 (90.2)	108 (87.8)	30 (100)	
Negative	15 (9.8)	15 (12.2)	0 (0)	
Preexisting conditions, N (%)				NA
Asthma	12 (7.8)	10 (8.1)	2 (6.7)	
Autoimmune disease	10 (6.5)	9 (7.3)	1(3.3)	
Diabetes	6 (3.9)	5 (4.1)	1(3.3)	
Hypertension	4 (2.6)	3 (2.4)	-	
Obesity	3 (2.0)	3 (2.4)	-	
Solid organ transplant	4 (2.6)	4 (3.3)	1 (3.3)	
Current smoking	9 (5.9)	9 (7.3)	-	
Severity of disease, N (%)				**0.004**
Asymptomatic or mild	60 (39.2)	43 (35.0)	17 (56.0)	
Moderate	67 (43.8)	62 (50.0)	5 (16.0)	
Severe or critical	26 (17.0)	18 (15.0)	8 (26.0)	
Semiquantative CT-SS median (IQR)	2 (0-7)	2 (0-6)	9 (0.8-17.3)	**0.022**
Qualitative CT-SS, N (%)				NA
Mild	44 (55.0)	42 (59.2)	2 (22.2)	
Moderate	29 (36.3)	26 (36.6)	3 (33.3)	
Severe	7 (8.8)	3 (4.2)	4 (44.4)	
Oxygen requirement, N (%)				0.110
Yes	30 (19.6)	21 (17.1)	9 (30.0)	
No	123 (80.4)	102 (82.9)	21 (70.0)	
IMV requirement, N (%)				**0.003**
Yes	7 (4.6)	2(1.6)	5 (17)	
No	3 (1.9)	1 (0.8)	2 (6.7)	
ICU requirement, N (%)				**<0.001**
Yes	10 (6.5)	3 (2.4)	7 (23.3)	
No	143 (93.5)	120 (97.6)	23 (76.7)	
HLOS, median (IQR)	4.0 (2.0-7.0)	4.0 (2.5-7.0)	5.0 (2.0-10.0)	0.680
Outcome, N (%)				0.620
Discharge	152 (99.3)	122 (99.2)	30 (100)	
Death	1 (0.7)	1 (0.8)	0 (0)	

*Antiviral medications include Favipravir, Lopinavir, Ritonavir, Remdesivir. † Heparin include either unfractionated or low molecular weight heparin PCR: Polymerase chain reaction, CT-SS: Computed tomography severity score, IMV: Invasive mechanical ventilation, ICU: Intensive care unit, HLOS: Hospital length of stay, NA: Not applicable, SD: Standard deviation, IQR: Interquartile ratio, N: Number of patients

Table 2. Laboratory characteristics of the study population

Variable*	All patients N=153	Nonpregnants N=123	Pregnants N=30	P value
Hb, g/dL	11.9 (1.6)	12.1 (1.6)	11.1 (1.0)	**0.001**
PLT, x10^3/uL	217.4 (78.4)	221 (73.5)	202.7 (96.0)	0.253
N, x10^3/uL	3.8 (2.5-5.3)	3.2 (2.4-4.7)	5.9 (4.7-7.0)	**<0.001**
L, x10^3/uL	1.2 (0.8-1.7)	1.2 (0.9-1.9)	0.9 (0.7-1.3)	**0.039**
NLR	2.9 (1.7-5.1)	2.3 (1.5-4.3)	5.8 (3.9-8.5)	**<0.001**
ESR, mm/h	30.0 (17-60)	24.0(16.0-54.0)	64.0(45.8-77.3)	**0.001**
CRP, mg/L	9.9 (3.1-40.3)	6.4 (3.1-31.9)	40.5 (9.9-114.5)	**<0.001**
D-Dimer, ng/mL	341.0(223.0-706.0)	289.(200.0-448.0)	1070.5 (686.3-2393.3)	**<0.001**
Fibrinogen, mg/dL	349.0 (249-485)	321.5 (207.8-456.5)	445 (378.5-611.0)	0.129
Ferritin, ng/mL	48.3 (27.4-124.2)	44.7 (23.9-117.5)	61.2 (35.8-136.3)	0.355
ProCT, ng/mL	0.05 (0.03-0.08)	0.04 (0.03-0.06)	0.08 (0.05-0.16)	**<0.001**
PT, sec	11.8 (11.2-12.5)	12.0 (11.4-12.7)	11.0 (10.6-11.7)	**<0.001**
PTT, sec	27.8 (25.5-30.9)	28.4 (25.5-30.9)	27.2 (24.8-30.9)	0.385
ALT, IU/L	15.6 (11.0-25.5)	16.0 (11.0-26.0)	13.0 (9.9-24.3)	0.133
AST, IU/L	21.0 (17.0-30.5)	21.4 (17.0-31.0)	19.8 (16.8-29.5)	0.379
ALP, IU/L	69.0 (51.0-99.5)	61.0 (47.0-83.3)	104.0 (92.0-130.5)	**<0.001**
GGT, IU/L	18.5 (10.0-36.0)	19.2 (10.0-41.0)	15 (7.0-27.0)	0.140
LDH, IU/L	217.0(182.0-283.0)	220.0 (181.3-270.8)	213.0 (186-337)	0.744
T.Bil, mg/dL	0.2(0.3-0.5)	0.3 (0.2-0.4)	0.4 (0.2-0.6)	**0.006**

*Hb and PLT are presented as mean (SD) and the rest of the variables are presented as median (IQR). Hb: Hemoglobin, PLT: Platelet, N: Neutrophile, L: Lymphocyte, NLR: Neutrophile lymphocyte ratio, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, ProCT: Procalcitonin, PT: Prothrombin time, PTT: Partial thromboplastin time, ALT: Alanine transaminase, AST: Aspartate transaminase, ALP: Alkaline phosphatase, GGT: Gamma glutamyl transaminase, LDH: Lactate dehydrogenase, T. Bil: Total bilirubine, SD: Standard deviation, SD: Standard deviation, IQR: Interquartile ratio.

Table 3. Characteristics of patients admitted to ICU

Variable	Critical patients N=10
Age, year, median (IQR)	33 (26.8-36.0)
Laboratory parameters, median (IQR)	
L, x10^3/uL	0.65 (0.48-1.40)
NLR	9.60 (5.20-17.60)
CRP, mg/L	162.5 (112.3-181.5)
D-Dimer, ng/mL	1039.5 (839.3-2163.8)
Ferritin, ng/mL	212.0 (79.6- 349.0)
Semiquantative CT-SS, median (IQR)	13.5 (8.5-19.8)
Qualitative CT-SS, n/N	
Mild	1/10
Moderate	4/10
Severe	5/10
SOFA score, median (IQR)	2.5 (2.0-4.8)
PaO_2/FiO_2 at ICU admission, mmHg, median (IQR)	143.5 (117.8-167.0)
Respiratory support, n/N	
Reservoir bag	1/10
HFNC	2/10
IMV	7/10
Days on IMV, median (IQR)	7 (1.8-21.8)
Septic shock, n/N	2/10
LOS in ICU, day, median (IQR)	9 (7-28)

L: Lymphocyte, NLR: Neutrophile lymphocyte ratio, CRP: C-reactive protein, CT-SS: Computed tomography severity score, SOFA: Sequential organ failure assessment, HFNC: High flow nasal canula, IMV: Invasive mechanical ventilation, LOS: Length of stay, ICU: Intensive care unit.

4. Discussion

In this cohort, the vast majority of pregnant cases were admitted in the third trimester, consistent with the previous data on COVID-19 and other respiratory viral infections during pregnancy. Urgent deliveries in our cases were almost due to worsening of the respiratory condition rather than primary obstetric indications. Although the pregnant women infected with COVID-19 had a worse clinical course than the nonpregnant matched control group, the mortality was low and similar in both groups. Our neonatal outcomes were also not as bad as expected.

All-cause early neonatal death rates of confirmed or suspected COVID-19 pregnant patients in 12 countries were found to be 0.2 to 0.3 percent. This rate is not higher than expected according to pre-COVID-19 national data (25).

In addition, a systematic review reported that the incidence of neonatal death in SARS-CoV-2 positive and negative pregnant women was similar (26). We reported one neonatal

death but no stillbirth or miscarriage among four premature births in 15 deliveries, which supports the current data. Nevertheless, severe maternal respiratory failure and hypoxia can disrupt placental blood flow, leading to preterm birth or miscarriage (27). Based on this knowledge, it is crucial to strictly implement infection control measures against viral respiratory illnesses in pregnant women.

The most common symptom at admission was cough in both groups, as in the CDC (Centers for Disease Control and Prevention) data (28). In other studies, fever or chills have been reported as the predominant symptom (15, 29, 30). Most notably, although the proportion of patients with either respiratory or non-respiratory symptoms and comorbidity was higher in the nonpregnant group, inversely, CT-SS was higher (9 points vs 2 points) and prognostic laboratory parameters including lymphocytopenia, NLR, CRP, ESR, and D-dimer were worse in the pregnant patients. We don't know the reason underlying this discrepancy; however, it could be attributed to the immune-compromised status of pregnancy and physiologic changes providing clinical vulnerability to severe viral lung infections and intolerance to hypoxia during pregnancy. Overexpression of ACE 2 receptor in pregnant women may also play a role in the severity of the disease, which is a hypothetical mechanism.

Based on large datasets, COVID-19 in pregnancy appears to be more severe in terms of morbidity than in nonpregnant women of reproductive age with COVID-19 (6, 7, 31). According to CDC data, the ICU admission rate was 10.5 vs 3.9, need for IMV was 2.9 vs 1.1 per 1000 cases in pregnant patients compared to nonpregnant cases (7). A prospective cohort study reported a propensity score-matched risks as 9.9 vs 6.4 percent for pneumonia and 13 vs 6.9 percent for ICU admission in pregnant and nonpregnant women with COVID-19, respectively (31). In this study, patients requiring mechanical ventilators (17% vs 1.6%) and ICU admission (23.3% vs 2.4%) were proportionally ten times higher in pregnant patients versus nonpregnant patients. A similar proportion was found between patients with high CT-SS as 44.0% vs 4.2% in pregnant patients and nonpregnant patients, respectively, indicating a crude correlation between CT severity and critical illness. Like other viral infections, early symptoms of COVID-19 may mimic physiologic dyspnea in pregnancy, which could cause a delay in diagnosis. In addition to above mentioned pregnancy-related factors, delayed diagnosis may also result in more severe disease (17, 32).

Current data suggest that mortality in either pregnant or nonpregnant women infected with COVID-19 is similar, between 0.8 and 1.5 percent (6, 7, 31). While we observed no mortality among the pregnant patients with COVID-19, the case fatality rate in nonpregnant patients of reproductive age was less than 1%. The case fatality rate of COVID-19 worldwide differs by country, age group, and setting and is changing over time. It has been reported to range from 0.5 to 10 % and higher than 20% in hospitalized patients (33, 34). Older age (≥35 years), obesity and pre-existing medical comorbidities (especially hypertension and diabetes or more than one comorbidity) are suggested to be the main risk factors for severe disease and death in pregnant women with COVID-19 (5, 35, 36). The absence of mortality in pregnant women in this cohort may be due to the younger age of mothers and lack of comorbidity. Also, there is a substantial amount of research showing that the

COVID-19 pandemic affects men more heavily in terms of disease incidence, hospitalization and death rates. The overall low mortality rates of COVID-19 infection in either pregnant or nonpregnant women of reproductive age may be due to the high progesterone level in women, particularly in pregnant women. There is preclinical evidence regarding the ability of progesterone, an immunomodulatory hormone with a steroid structure, to repair lung damage in respiratory viral infections (37). Nevertheless, this is an area of uncertainty that merits further investigation.

A recent metanalysis on prognostic factors for mortality and severity of COVID-19 disease showed that a high SOFA score defined as more than 2 points is related to a 7.3% increase in mortality and a 63% increase in severe disease with moderate and low certainty of evidence respectively (38). In this study, the SOFA score was median of 2.5 points, which was predominantly obtained from PaO2/FiO2, indicating that organ failure is mostly confined to the respiratory system rather than the multiorgan involvement. However, there was a remarkable deviation in lymphocytopenia, CRP, D-dimer, NLR, and ferritin parameters in patients admitted to the ICU, which are related to a worse prognosis (39). PaO2/FiO2 ratio was median 143 mmHg, consistent with moderate ARDS according to Berlin definition (40). The only patient in the study who died was nonpregnant and had restrictive lung disease due to scoliosis, and the SOFA score at admission was 12 points.

The factors limiting the study are the retrospective method and single-center data. Besides, the sample size of the study is not large enough to extrapolate the data on mortality and morbidity to the general population. However, it contributes to the accumulation of new data for literature on COVID-19 during pregnancy. Due to missing data, we could not make a correlation analysis between CT-SS and clinical or laboratory parameters.

Pregnant patients infected with COVID-19 seem at higher risk for severe or critical illness than nonpregnant control patients with COVID-19. Due to increased morbidity, pregnant women should be approached more alertly regarding screening, isolation, and treatment. Studies designed with a larger sample size and higher quality are necessary to obtain more conclusive data on the prognosis of COVID-19 in these patient groups.

Conflict of interest
All authors state that there is no potential conflict of interest.

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Authors' contributions
Concept: O.K., M.P., N.T.T., E.K., M.D., M.E., İ.B., D.G. Design: O.K., M.P., N.T.T., E.K., M.D., M.E., İ.B., D.G., Data Collection or Processing: M.P., N.T.T., E.K., Analysis or Interpretation: O.K., M.P., Literature Search: O.K., M.P., N.T.T., Writing: O.K.

References

1. Metz TD, Clifton RG, Hughes BL, Sandoval G, Saade GR, Grobman WA, et al. Disease Severity and Perinatal Outcomes of Pregnant Patients With Coronavirus Disease 2019 (COVID-19). Obstet Gynecol. 2021 Apr 1;137(4):571-580.
2. Mullins E, Hudak ML, Banerjee J, Getzlaff T, Townson J, Barnette K, et al. Pregnancy and neonatal outcomes of COVID-19: coreporting of common outcomes from PAN-COVID and AAP-SONPM registries. Ultrasound Obstet Gynecol. 2021 Apr;57(4):573-581.
3. Huntley BJF, Mulder IA, Di Mascio D, Vintzileos WS, Vintzileos AM, Berghella V, et al. Adverse Pregnancy Outcomes Among Individuals With and Without Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): A Systematic Review and Meta-analysis. Obstet Gynecol. 2021 Apr 1;137(4):585-596.
4. Chinn J, Sedighim S, Kirby KA, Hohmann S, Hameed AB, Jolley J, et al. Characteristics and Outcomes of Women With COVID-19 Giving Birth at US Academic Centers During the COVID-19 Pandemic. JAMA Netw Open. 2021 Aug 2;4(8):e2120456.
5. Kasehagen L, Byers P, Taylor K, Kittle T, Roberts C, Collier C, et al. COVID-19-Associated Deaths After SARS-CoV-2 Infection During Pregnancy - Mississippi, March 1, 2020-October 6, 2021. MMWR Morb Mortal Wkly Rep. 2021 Nov 26;70(47):1646-1648.
6. Allotey J, Stallings E, Bonet M, Yap M, Chatterjee S, Kew T, et al. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. BMJ. 2020 Sep 1;370:m3320.
7. Zambrano LD, Ellington S, Strid P, Galang RR, Oduyebo T, Tong VT, et al. Update: Characteristics of Symptomatic Women of Reproductive Age with Laboratory-Confirmed SARS-CoV-2 Infection by Pregnancy Status - United States, January 22-October 3, 2020. MMWR Morb Mortal Wkly Rep. 2020 Nov 6;69(44):1641-1647.
8. Badr DA, Mattern J, Carlin A, Cordier AG, Maillart E, El Hachem L, et al. Are clinical outcomes worse for pregnant women at ≥20 weeks' gestation infected with coronavirus disease 2019? A multicenter case-control study with propensity score matching. Am J Obstet Gynecol. 2020 Nov;223(5):764-768.
9. Qeadan F, Mensah NA, Tingey B, Stanford JB. The risk of clinical complications and death among pregnant women with COVID-19 in the Cerner COVID-19 cohort: a retrospective analysis. BMC Pregnancy Childbirth. 2021 Apr 16;21(1):305.
10. DeBolt CA, Bianco A, Limaye MA, Silverstein J, Penfield CA, Roman AS, et al. Pregnant women with severe or critical coronavirus disease 2019 have increased composite morbidity compared with nonpregnant matched controls. Am J Obstet Gynecol. 2021 May;224(5):510.e1-510.e12.
11. Lokken EM, Huebner EM, Taylor GG, Hendrickson S, Vanderhoeven J, Kachikis A, et al. Disease severity, pregnancy outcomes, and maternal deaths among pregnant patients with severe acute respiratory syndrome coronavirus 2 infection in Washington State. Am J Obstet Gynecol. 2021 Jul;225(1):77.e1-77.e14.
12. Dawood FS, Varner M, Tita A, Newes-Adeyi G, Gyamfi-Bannerman C, Battarbee A et al. Incidence, Clinical Characteristics, and Risk Factors of SARS-CoV-2 Infection among Pregnant Individuals in the United States. Clin Infect Dis. 2021 Aug 19:ciab713.
13. Gulersen M, Rochelson B, Shan W, Wetcher CS, Nimaroff M, Blitz MJ. Severe maternal morbidity in pregnant patients with SARS-CoV-2 infection. Am J Obstet Gynecol MFM. 2022 Jul;4(4):100636.
14. McClymont E, Albert AY, Alton GD, Boucoiran I, Castillo E, Fell DB, et al. Association of SARS-CoV-2 Infection During Pregnancy With Maternal and Perinatal Outcomes. JAMA. 2022 May 24;327(20):1983-1991.
15. Chen H, Guo J, Wang C, Luo F, Yu X, Zhang W, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. Lancet. 2020 Mar 7;395(10226):809-815.
16. Tamanna S, Clifton VL, Rae K, van Helden DF, Lumbers ER, Pringle KG. Angiotensin Converting Enzyme 2 (ACE2) in Pregnancy: Preeclampsia and Small for Gestational Age. Front Physiol. 2020 Sep 30;11:590787.
17. Narang K, Enninga EAL, Gunaratne MDSK, Ibirogba ER, Trad ATA, Elrefaei A, et al. SARS-CoV-2 Infection and COVID-19 During Pregnancy: A Multidisciplinary Review. Mayo Clin Proc. 2020 Aug;95(8):1750-1765.
18. Pineles BL, Goodman KE, Pineles L, O'Hara LM, Nadimpalli G, Magder LS, et al. In-Hospital Mortality in a Cohort of Hospitalized Pregnant and Nonpregnant Patients With COVID-19. Ann Intern Med. 2021 Aug;174(8):1186-1188.
19. Leung C, de Paiva KM. Is pregnancy a risk factor for in-hospital mortality in reproductive-aged women with SARS-CoV-2 infection? A nationwide retrospective observational cohort study. Int J Gynaecol Obstet. 2022 Apr;157(1):121-129.
20. Hsu AL, Ohler AM, Goldstein A, Truong S, Tang CY, Wan XF et al. Coronavirus Disease 2019 (COVID-19) Disease Severity: Pregnant vs Nonpregnant Women at 82 Facilities. Clin Infect Dis. 2022 Feb 11;74(3):467-471.
21. National Institutes of Health. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. Available from: https://www.covid19treatmentguidelines.nih.gov/
22. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315(8):801-810.
23. Pan F, Ye T, Sun P, Gui S, Liang B, Li L, et al. Time Course of Lung Changes at Chest CT during Recovery from Coronavirus Disease 2019 (COVID-19). Radiology. 2020;295(3):715-721.

24. Tabatabaei SMH, Rajebi H, Moghaddas F, Ghasemiadl M, Talari H. Chest CT in COVID-19 pneumonia: what are the findings in mid-term follow-up? Emerg Radiol. 2020;27(6):711-719.

25. Mullins E, Hudak ML, Banerjee J, Getzlaff T, Townson J, Barnette K et al. Pregnancy and neonatal outcomes of COVID-19: coreporting of common outcomes from PAN-COVID and AAP-SONPM registries. Ultrasound Obstet Gynecol. 2021 Apr;57(4):573-581.

26. Huntley BJF, Mulder IA, Di Mascio D, Vintzileos WS, Vintzileos AM, Berghella V et al. Adverse Pregnancy Outcomes Among Individuals With and Without Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): A Systematic Review and Meta-analysis. Obstet Gynecol. 2021 Apr 1;137(4):585-596.

27. Wong SF, Chow KM, Leung TN, Ng WF, Ng TK, Shek CC, et al. Pregnancy and perinatal outcomes of women with severe acute respiratory syndrome. Am J Obstet Gynecol. 2004;191(1):292-297.

28. Ellington S, Strid P, Tong VT, Woodworth K, Galang RR, Zambrano LD, et al. Characteristics of Women of Reproductive Age with Laboratory-Confirmed SARS-CoV-2 Infection by Pregnancy Status - United States, January 22-June 7, 2020. MMWR Morb Mortal Wkly Rep. 2020;69(25):769-775.

29. Di Mascio D, Khalil A, Saccone G, Rizzo G, Buca D, Liberati M, et al. Outcome of coronavirus spectrum infections (SARS, MERS, COVID-19) during pregnancy: a systematic review and meta-analysis. Am J Obstet Gynecol MFM. 2020;2(2):100107.

30. Liu D, Li L, Wu X, Zheng D, Wang J, Yang L, et al. Pregnancy and Perinatal Outcomes of Women With Coronavirus Disease (COVID-19) Pneumonia: A Preliminary Analysis . AJR Am J Roentgenol. 2020;215(1):127-132.

31. Martinez-Portilla RJ, Sotiriadis A, Chatzakis C, Torres-Torres J, Espino Y Sosa S, Sandoval-Mandujano K, et al.Pregnant women with SARS-CoV-2 infection are at higher risk of death and pneumonia: propensity score matched analysis of a nationwide prospective cohort (COV19Mx). Ultrasound Obstet Gynecol. 2021 Feb;57(2):224-231.

32. Society for Maternal-Fetal Medicine. Management considerations for pregnant patients with COVID-19. Available from: https://s3.amazonaws.com/cdn.smfm.org/media/2334/SMFM_COVID_Management_of_COVID_pos_preg_patients_4-29-20_final.pdf.

33. Centre for Evidence-Based Medicine. Global COVID-19 Case Fatality Rates. Available from: https://www.cebm.net/covid-19/global-covid-19-case-fatality-rates/

34. International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC). Available from: https://media.tghn.org/medialibrary/2020/05/ISARIC_Data_Platform_COVID- 19_Report_19MAY20.pdf.

35. Karimi L, Makvandi S, Vahedian-Azimi A, Sathyapalan T, Sahebkar A. Effect of COVID-19 on Mortality of Pregnant and Postpartum Women: A Systematic Review and Meta-Analysis. J Pregnancy. 2021;2021:8870129. Published 2021 Mar 5.

36. Galang RR, Newton SM, Woodworth KR, Griffin I, Oduyebo T, Sancken CL et al. Risk Factors for Illness Severity Among Pregnant Women With Confirmed Severe Acute Respiratory Syndrome Coronavirus 2 Infection-Surveillance for Emerging Threats to Mothers and Babies Network, 22 State, Local, and Territorial Health Departments, 29 March 2020-5 March 2021. Clin Infect Dis. 2021 Jul 15;73(Suppl 1):S17-S23.

37. Wastnedge EAN, Reynolds RM, van Boeckel SR, Stock SJ, Denison FC, Maybin JA, et al. Pregnancy and COVID-19. Physiol Rev. 2020;1;101(1):303-318.

38. Izcovich A, Ragusa MA, Tortosa F, Lavena Marzio MA, Agnoletti C, Bengolea A, et al. Prognostic factors for severity and mortality in patients infected with COVID-19: A systematic review. PLoS One. 2020;15(11):e0241955.

39. Pierce-Williams RAM, Burd J, Felder L, Khoury R, Bernstein PS, Avila K, et al. Clinical course of severe and critical coronavirus disease 2019 in hospitalized pregnancies: a United States cohort study. Am J Obstet Gynecol MFM. 2020;2(3):100134.

40. Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA. 2012;307(23):2526-2533.