Clinical and radiologic characteristics of symptomatic pregnant women with COVID-19 pneumonia

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Abstract

Objective: To describe the radiological features, diagnostic accuracy and features of imaging studies and their relation with clinical course of Coronavirus disease-2019 (COVID-19) pneumonia in pregnant women.

Material and Methods: The clinical, laboratory and radiological features of symptomatic pregnant women suspected of COVID-19 were retrospectively reviewed. Chest radiography (CXR) and chest computed tomography (CT) findings of COVID-19 in pregnant women were identified.

Results: Fifty-five of eighty-one pregnant women were included in the final analysis. The most common admission symptoms were dry cough (45.4%), fever (29.1%) and dyspnea (34.5%). Radiological imaging studies were performed in 34 (61.8%) patients. Fourteen (66.7%) of the laboratory-confirmed COVID-19 patients had parenchymal abnormalities on CXR, and most common abnormalities were airspace opacities (61.9%) and prominent bronchovascular shadows (28.6%). Seventeen (85.0%) of the patients had parenchymal abnormalities consistent with COVID-19 on their chest CT. Chest CT most commonly showed bilateral (88.2%), multilobe (100%) involvement; peripheral and central distribution (70.6%); patchy-shape (94.1%) and ground-glass opacity (94.1%). The sensitivity of CXR and chest CT was calculated as 66.7% and 83.3%, respectively. Preterm birth rate was 41.2% (n=7/17). Five (9.1%) of the 55 pregnant women admitted to the intensive care unit, three of those developed acute respiratory distress syndrome and one died.

Conclusion: This study describes the main radiological features of symptomatic pregnant women infected with COVID-19. The refusal rate among pregnant women for the imaging modalities involving ionizing radiation was high but these had high sensitivity for COVID-19 diagnosis. The preterm birth and cesarean section rates were observed as remarkably increased. (J Turk Ger Gynecol Assoc 2021; 22: 196-205)

Keywords: COVID-19, pregnancy, computed tomography, chest radiography, radiology

Introduction

Pregnancy is known to cause significant anatomical and physiological changes in respiratory function and these changes can increase susceptibility to respiratory tract infections and can quickly lead to respiratory failure (1). In addition, the modulation of the immune system during pregnancy leaves pregnant women vulnerable to viral infections, which may lead to even more severe symptoms (2). Previous studies have also shown that severe acute respiratory syndrome (SARS) and middle east respiratory syndrome infections were associated with serious maternal disease, maternal deaths, and spontaneous abortions (3-5). Pregnant women are at increased risk for severe illness from Coronavirus disease-2019 (COVID-19) compared to non-

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pregnant people (6,7). Additionally, there may be an increased risk of adverse pregnancy outcomes, such as preterm birth, among pregnant women with COVID-19 (8,9). Moreover, the high refusal rate of imaging modalities involving ionizing radiation during pregnancy and the risks to fetuses present as a limiting factor in the diagnosis and treatment of pregnant women, making the diagnostic process more difficult when compared to the non-pregnant population (10). Therefore, pregnant women constitute a vulnerable group that requires special attention in the diagnosis and treatment of COVID-19.

The most commonly used reference standard in the diagnosis of COVID-19 is the reverse transcription polymerase chain reaction (RT-PCR) test. However, due to the technical limitations of the test and its relatively high false negative rate, radiological imaging including chest CT and chest radiography (CXR) play an important role in the diagnosis and evaluation of pregnant women suspected with COVID-19 infection (11,12). Chest CT has been reported to be more sensitive than other modalities in the diagnosis of COVID-19 pneumonia (13).

Robust data concerning radiological and clinical features of pregnant women with COVID-19 pneumonia is scarce in the literature. This study aimed to identify the demographic characteristics and evaluate the clinical, laboratory, and radiological findings of symptomatic pregnant women with COVID-19 pneumonia.

Material and Methods

Patient population and study design

This retrospective study was conducted at two tertiary health care centers dedicated to treating severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) pandemic between March 15th and September 1th, 2020. Symptomatic pregnant women suspected of COVID-19 infection were included in the study. Patients who were tested for SARS-CoV-2 infection for universal screening purposes were not included in the study (14). Patients who refused chest CT or CXR with negative PCR test result were excluded. Those patients were managed according to the national guidelines (15). Pregnant women with COVID-19 infection confirmed either by PCR-testing or imaging studies were included to the final analysis (Figure 1). The disease was classified as mild, moderate and severe according to its clinical severity (15).

The demographic characteristics, clinical signs and symptoms, and laboratory results of the patients were obtained from the patients' electronic health records. Clinical symptoms, including fever ($\geq$37.3 °C), cough, dyspnea, sore throat, and fatigue, were assessed in terms of COVID-19. RT-PCR tests were performed using combined swab samples taken from the oropharynx and the nasopharynx of the patients, were used to confirm SARS-CoV-2 infection. The radiological examinations (CT and/or CXR) of the pregnant women were re-evaluated,
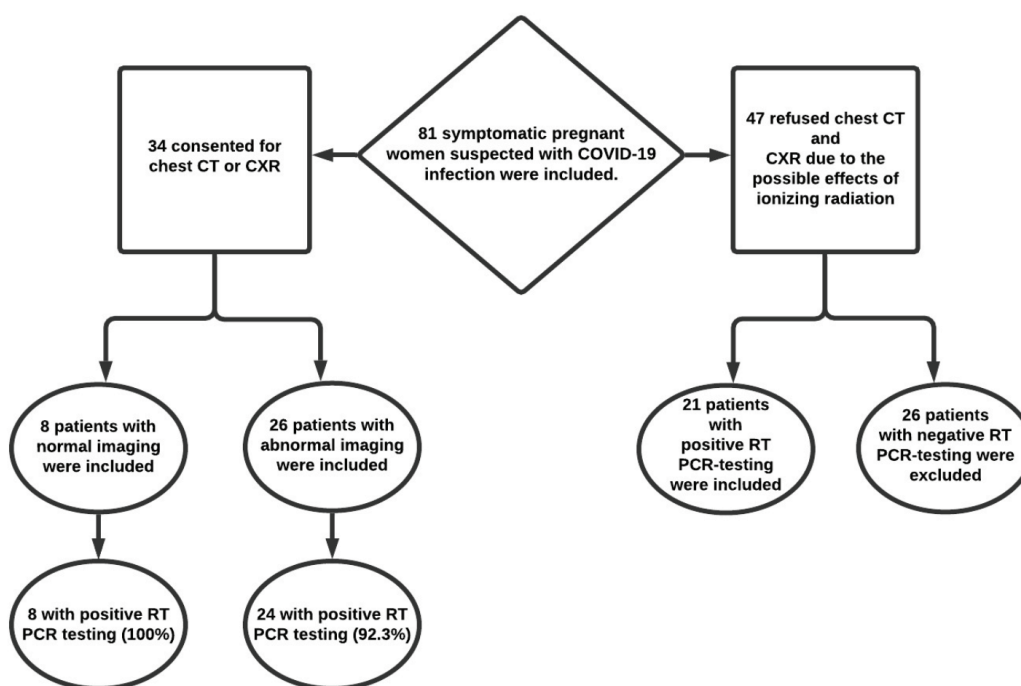
Figure 1. Flowchart of the study

CT: Computed tomography, CXR: Chest radiography, COVID-19: Coronavirus disease-2019, RT-PCR: Reverse transcription polymerase chain reaction

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independent from and blinded to the initial report. The study was approved by the Ethical Committee of the University of Health Sciences Turkey, Kartal Koşuyolu Training and Research Hospital (approval number: 2020.4/07-312) and the national health authorities.

Radiological imaging

Low-dose imaging protocol was followed. Radiological imaging criteria were met if at least two of the following symptoms were present: a fever above 38.3 °C, a respiratory rate of 22 breaths/minute and above, saturation of peripheral oxygen (SpO$_2$) below 93%, or severe dyspnea. The possible effects of radiation exposure on the fetus were explained in detail and written consent was obtained from each patient. The choice of imaging method (CXR and/or CT) was decided together with the patient, considering diagnostic performance of imaging methods, the pregnancy trimester and the clinical condition of the patient.

CXR was performed using a digital X-ray machine (DRGEM Radiography System, South Korea). The CXR parameters were as follows: 75-110 kVp, 4-8 mAs, and detector size 35x43 cm with grid. During the examination, the abdomen and pelvis were protected with a lead sheath. The effective dose for CXR images did not exceed 0.07 mSv (millisieverts).

Chest CT was performed in all patients using a 16 or 128-slice CT scanner (Optima 520 CT, GE company or Ingenuity Core 128, Philips Healthcare). CT images were obtained with the patient in the supine position at full inspiration and without contrast medium. For the pregnant participants, 80 kV tube voltage, 50 mAs automatic tube current modulation, 5 mm slice thickness, 5 mm slice interval, a noise index of 16, 36.0 DFOV, and 512 x 512 matrix were used. The thyroid, abdomen, and pelvis were protected by a lead sheath. The dose-length product was 25-100 mGy.

Image analysis

The reconstructed images were transmitted to the workstation and picture archiving and communication systems for multiplanar reconstruction post-processing. The chest radiographs and chest CT images of the cases were evaluated by three radiologists, blinded to RT-PCR results, at the radiology workstation. In cases where the three radiologists evaluated differently, the result was reached by consensus.

The CXR findings were classified as typical, indeterminate, atypical, and negative for COVID-19 (16). For statistical evaluation, typical and indeterminate groups were considered COVID-19 positive, and atypical and negative groups were accepted as COVID-19 negative. An example of chest CXR findings is shown in Figure 2.

CT findings were categorized as non-COVID-19, indeterminate COVID-19, probable COVID-19, and classic COVID-19 according to the COVID-19 infection version 2 of the British Society of Thoracic Imaging (17). For statistical evaluation, non-COVID-19 cases were categorized as CT negative group, while indeterminate COVID-19, probable COVID-19 and classic COVID-19 cases were categorized as CT positive group.

The distribution in the lung, shape, location, appearance, and size of the largest lesion were recorded. In addition, vascular enlargement, intralobular/interlobular septal thickening, air bronchogram, subpleural curvilinear lines, parenchyma findings such as bronchial wall thickening, fibrous bands, halo sign, and reversed halo sign were noted. Extrapulmonary findings such as pleural effusion, pleural thickening, and enlarged lymph nodes were also included. In the chest CT positive cases, CT severity index according to the degree of lesion distribution was calculated, as described previously (18).

Statistical analysis

Descriptive analyses were performed for the characteristics of the patients. The normally distributed continuous random variables were expressed as the mean ± standard deviation
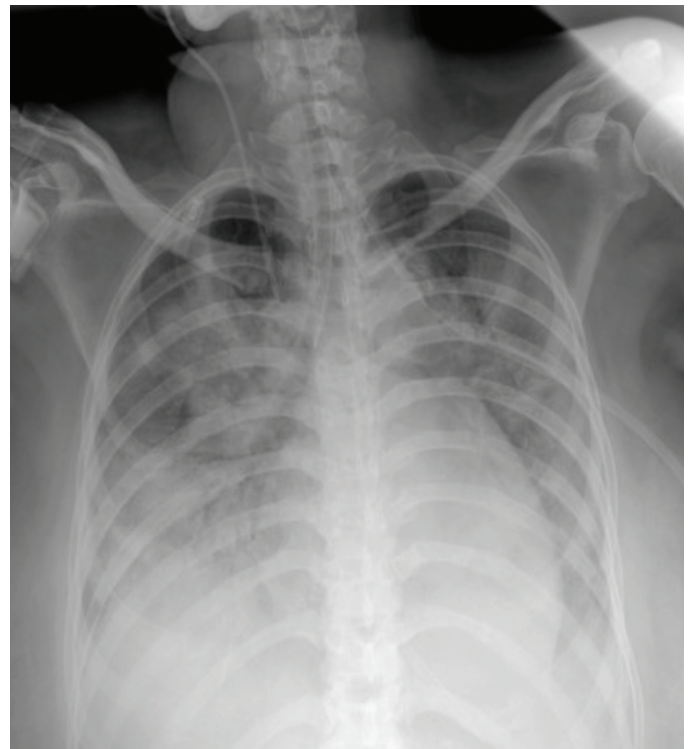
Figure 2. A 35-year-old, laboratory-confirmed COVID-19, pregnant woman with 25 weeks of pregnancy presented with fever and dyspnea. The patient developed hypoxic respiratory failure and was admitted to intensive care unit. Anteroposterior chest radiograph shows an ARDS pattern with ill-defined alveolar consolidation bilaterally in the predominantly lower zones

COVID-19: Coronavirus disease-2019, ARDS: Acute respiratory distress syndrome

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and categorical variables are expressed as percentages. Fisher's exact test was used to compare the severity of the disease between trimesters and the One-Way ANOVA test was used to compare the severity of pneumonia involvement (CT severity index). The sensitivity of CXR and chest CT was calculated for the diagnosis of COVID-19 disease, using RT-PCR as reference. SPSS 17.0 (IBM Inc., Armonk, NY, USA) was used for the statistical analyses.

Results

Eighty-one pregnant women suspected with COVID-19 infection were enrolled. Forty-seven patients (58.0%) refused chest CT and CXR due to the risks of receiving ionizing radiation when pregnant. Out of these, 26 patients who had negative RT-PCR-testing were excluded. Fifty-five pregnant women with COVID-19 infection confirmed either with RT-PCR-testing or imaging studies were included in the final analysis. Pregnant women were confirmed as having COVID-19 by RT-PCR alone (n=29), imaging studies alone (n=2), and both (n=24). Radiological imaging studies were performed in 34 (61.8%) patients. The positivity rate in PCR-testing among patients with abnormal imaging was 92.3% (n=24/26).

Demographic, clinical and laboratory characteristics of pregnant women are given in Table 1. The first, second, and third trimester distribution of pregnant women at the time of presentation were n=8 (14.6%), n=24 (43.6%), and n=23 (41.8%), respectively. The patients' clinical condition was mild in eight (100%) pregnant women in the first trimester. In the second trimester, 20 (83.3%) cases were mild, 3 (12.5%) cases were moderate, and 1 (4.2%) case was severe, in the third trimester 18 (78.3%) cases were mild, 2 (8.7%) cases were moderate, and 3 (13.0%) cases were severe. Although mild and severe cases were more frequent in the third trimester, the difference between trimesters was not statistically significant (p=0.672). CT severity index of pregnant women in first, second, and third trimesters was 3.7, 7.5, and 6.3, respectively. Although pneumonia involvement (CT severity index) was higher in the second and third trimester, the difference between trimesters did not reach a statistically significant level (p=0.697). During the study period, 12 cases gave birth by cesarean (C/S), and five cases had a normal spontaneous vaginal delivery, for a total of 17 cases delivered (seven preterm, 10 term), and one case of missed abortus at seven weeks. The remaining 37 were still pregnant during the study.

Five of 55 patients (9.1%) were admitted to the intensive care unit (ICU). One patient and the fetus died in her 22nd weeks of gestation due to acute respiratory distress syndrome (ARDS). CXR detail of that patient was common airspace opacities more prominent in the lower lobes, compatible with ARDS (Figure 2).

Repeated RT-PCR testing was performed in nine of 34 (26.5%) patients whose first RT-PCR test was negative. Second RT-PCR test increased the COVID-19 positivity rate from 58.0% (47/81) to 65.4% (53/81). There was no vertical transmission.

The radiological classification of imaging studies is summarized in Table 2. Twenty-one (61.8%) of 34 patients underwent CXR and 20 of them underwent low-dose chest CT. In seven patients,

Table 1. Demographic, clinical and laboratory characteristics of pregnant women at presentation (n=55)

Patient demographics		
Age mean ± SD (range)		29.7±6.4 (19-53)
RT-PCR positivity n (%)		53/81 (65.4%)
Presenting findings n (%)		
Fever (>37.3 °C)		16 (29.1%)
Dry cough		25 (45.4%)
Dyspnea		19 (34.5%)
Fatigue		11 (20.0%)
Sore throat		17 (30.9%)
Anosmia		5 (9.1%)
Suspicious contact		26 (47.3%)
Laboratory tests		
WBC	Low	1 (1.8%)
	Normal	43 (78.2%)
	High	11 (20.0%)
Lymphocyte	Low	23 (41.8%)
	Normal	32 (58.2%)
	High	0 (0%)
CRP (n=52)	Normal	18 (34.6%)
	High	34 (65.4%)
LDH (n=43)	Normal	26 (60.5%)
	High	17 (39.5%)

SD: Standard deviation, RT-PCR: Reverse transcription polymerase chain reaction, WBC: White blood cell count, CRP: C-reactive protein, LDH: Lactate dehydrogenase

Table 2. Radiologic imaging of patients (n=34)

Chest radiography classification (n=21)	
Negative	6 (28.6%)
Atypical	1 (4.7%)
Indeterminate	9 (42.9%)
Typical	5 (23.8%)
Chest CT classification (n=20)	
Normal	3 (15.0%)
Non-COVID-19	0 (0.0%)
Indeterminate COVID-19	2 (10.0%)
Probable COVID-19	1 (5.0%)
Classic COVID-19	14 (70.0%)

CT: Computed tomography, COVID-19: Coronavirus disease-2019

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both CXR and chest CT were performed. The sensitivity of CXR and chest CT was calculated as 66.7% [95% confidence interval (CI) 43.0 to 85.4%] and 83.3% (95% CI 58.6 to 96.4%), respectively, using RT-PCR as reference. Fourteen of the 21 COVID-19 patients (66.7%) had parenchymal abnormalities in CXR. Twelve had bilateral and one had unilateral airspace opacities (consolidation or ground-glass opacity) while the last had prominent bronchovascular shadows only. The distribution of the airspace opacities was central and peripheral in five cases, central in four cases, and peripheral in five cases. Prominent bronchovascular shadows were observed in six cases, five of which were bilateral. The radiological findings of abnormal chest CT were given in Table 3.

Discussion

This study defined the clinical presentation, laboratory and radiological features of symptomatic pregnant women diagnosed with SARS-CoV-2 infection either by RT-PCR testing or imaging studies.

Imaging features of COVID-19 infection in pregnant women, as in the non-pregnant population, are predominantly peripheral and bilateral patchy ground glass opacities with or without consolidation (12,19-21). In this study, the radiological features were commonly seen in both central and peripheral lung tissues. This difference might be related to the phase of the disease or the diseases might progress rapidly in pregnant women (20). The other imaging features of COVID-19 were similar with previous studies (12,20,21).

Three of every five pregnant women did not give consent for imaging studies involving ionizing radiation in this study. To the best of our knowledge, this finding was not previously reported. Royal College of Obstetricians and Gynecologists guidelines state that maternal health is more important than fetal health in pregnant patients (2). Therefore, radiological examination can be performed in pregnant women while exposure to ionizing radiation should be as low as reasonably achievable. In routine chest CT, the radiation dose is approximately 4-7 mGy, and the radiation dose of a CXR or low-dose chest CT is far below the accepted limit for a fetus (22). Radiation exposure of less than 100 mGy in utero after implantation has no proven deterministic effect on the fetus. However, stochastic effects of cancer induction are known to exist, albeit slightly, and increase in proportion to dose (23). The use of radiological examinations in the diagnosis of COVID-19 pneumonia in pregnant patients requires special attention due to the risk of fetal teratogenicity caused by radiation exposure. Lung ultrasound may provide a good solution for patients who refuse chest CT or CRX (14,24). The diagnostic performance of CXR in detecting COVID-19 pneumonia is lower than that of CT, and the sensitivity was reported to be 33-69% in studies involving few non-pregnant

cases (25). Chest CT sensitivity was reported to be as high as 94% in a meta-analysis (26). Similarly, the sensitivity of CXR in detecting COVID-19 pneumonia was found to be 66.7% in this study, whereas chest CT sensitivity was 86.6%. The authors postulate that CXR can be used as the initial radiological examination for symptomatic pregnant patients with COVID-19 considering its relatively lower radiation dose and moderate sensitivity. However, a normal CXR cannot rule out COVID-19. In this study, ARDS development was detected in the CXR in one case and in the chest CT in two cases and, one of these cases involved concomitant pneumothorax and pneumomediastinum (Figure 3). This severe patient was treated in the ICU and required mechanical ventilation. Although spontaneous pneumomediastinum is a rare complication of COVID-19, the mechanism of pneumomediastinum is not clear (27). These individual cases have highlighted the importance of radiologic imaging, not only in diagnosing COVID-19 pneumonia, but also in detecting accompanying complications of the disease.

The most common admission symptoms of the patients included in the study were dry cough, fever, and dyspnea, which were similar with those in the non-pregnant population. Laboratory findings showed a normal leukocyte count with lymphocytopenia, and increased C-reactive protein and lactate dehydrogenase concentrations, which were similar to the findings in non-pregnant population (28,29).

In our study group, six of the nine pregnant women whose first RT-PCR test was negative, had a positive result on the second RT-PCR test. Although the RT-PCR test is accepted as a reference in the diagnosis of COVID-19, the sensitivity of the test is low. The positivity rate of the first test is 60-71%, and the positivity rate increases with subsequent tests (30). Thus, a diagnosis of COVID-19 should not be ruled out in pregnant patients with a single negative RT-PCR test result. Considering the method used to obtain the sample, and low sensitivity due to technical reasons, repetition of the test should not be avoided in cases where the first test is negative if clinical, laboratory, or radiological findings are consistent.

It is shown that COVID-19 in pregnancy was associated with maternal morbidity and preterm birth and required a high rate (8%) of intensive care admission (6,9). Similarly, in this study 54.3% of all births were performed with cesarean section and the preterm birth rate was 58.8%. In addition, 9.1% of the pregnant patients included in the study were admitted to the ICU, three of whom developed ARDS and one of them died. Some of the studies conducted at the beginning of the pandemic claim that the course of COVID-19 during pregnancy is not different to non-pregnant cases (31,32). Contrary to these studies, our preliminary results suggest that clinical course of the COVID-19 in pregnancy seems more severe, similar to more recent studies (7,33). Similar to our study results, the

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Table 3. Case-based chest CT findings of pregnant women with COVID-19

Case	1	2	3	4	5	6	7	8
RT-PCR	+	+	+	+	+	+	+	+
CT classification Classic COVID-19 Probable COVID-19 Indeterminate COVID-19 Non- COVID-19	Classic	Classic	Classic	Classic	Classic	Classic	Classic	Classic
Lung involment Bilateral (B/L) Right Left	B/L	B/L	B/L	B/L	B/L	B/L	B/L	B/L
Number of lobes involved (1-5)	5	5	5	5	4	5	5	5
Max diameter of lession (cm)	2.1	5.5	3.5	6.7	4.7	3.7	6.6	2.2
CT severty index Mild ($\leq$5) Moderate (6-11) Severe ($\geq$12)	Severe (18)	Moderate (7)	Severe (12)	Moderate (6)	Moderate (6)	Moderate (10)	Moderate (7)	Moderate (7)
Distrubition of lesions Peripheral (P) Central (C) Peripheral and central (P&C)	P&C	P&C	P&C	P&C	P&C	P&C	P&C	P&C
Shape of lesions Patchy Diffuse	Patchy	Patchy	Patchy	Patchy	Patchy	Diffuse	Patchy	Patchy
Appeareance of lesions Ground glass opacity (GGO) Consolidation (C) GGO and consolidation (GGO&C)	GGO&C	GGO&C	GGO	GGO&C	GGO&C	GGO&C	GGO&C	GGO
CT Paranchimal findings								
Vasculer enlargement	+	-	+	-	-	+	-	-
Intralobular reticular density	+	-	-	-	+	+	-	-
Bronchial wall thickening	+	-	-	-	-	-	+	-
Subpleural curvilineer lines	+	-	-	-	-	-	+	-
Air bronchogram	-	-	-	+	-	+	-	-
Fibrous band	+	-	-	+	+	-	-	-
Subpleural sparing	-	+	+	-	-	+	+	-
Halo sign	-	-	-	-	-	+	-	-
Reversed halo sign	-	-	+	-	-	-	-	-
Extrapulmonary manifesation								
Pleural thickening	-	-	-	-	-	-	-	-
Lymphadenopaty	-	-	-	-	-	-	-	-
Pleural effusion	-	-	-	-	-	+	-	-
Pneumomediastenum and Pneumothorax	-	-	-	-	-	-	-	-
CT: Computed tomography, RT-PCR: Reverse transcription polymerase chain reaction, COVID-19: Coronavirus disease-2019								

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Table 3. Continued

Case	9	10	11	12	13	14	15	16	17
RT-PCR	+	+	+	+	+	+	+	-	-
CT classification Classic COVID-19 Probable COVID-19 Indeterminate COVID-19 Non- COVID-19	Classic	Classic	Indeter-minate	Classic	Classic	Classic	Classic	Indeter-minate	Probable
Lung involment Bilateral (B/L) Right Left	B/L	Right	B/L	B/L	B/L	B/L	B/L	B/L	Right
Number of lobes involved (1-5)	5	2	2	4	5	3	5	2	2
Max diameter of lession (cm)	2.3	5.1	4.7	3.4	8	4.3	9.2	3.1	1.0
CT severty index Mild (≤5) Moderate (6-11) Severe (≥12)	Mild (5)	Mild (4)	Mild (2)	Mild (4)	Modarete (6)	Mild (3)	Severe (22)	Mild (2)	Mild (2)
Distrubition of lesions Peripheral (P) Central (C) Peripheral and central (P&C)	P&C	P	P	P	P&C	P	P&C	P	P&C
Shape of lesions Patchy Diffuse	Patchy	Patchy	Patchy	Patchy	Patchy	Patchy	Diffuse	Patchy	Patchy
Appeareance of lesions Ground glass opacity (GGO) Consolidation (C) GGO and consolidation (GGO&C)	GGO	GGO	C	GGO&C	GGO	GGO	GGO&C	GGO	GGO&C
CT Paranchimal findings									
Vasculer enlargement	-	+	-	+	+	+	-	-	-
Intralobular reticular density	-	-	-	-	+	-	+	-	-
Bronchial wall thickening	-	-	-	-	-	-	-	-	-
Subpleural curvilineer lines	-	-	-	-	-	-	-	-	-
Air bronchogram	-	-	+	-	-	-	+	-	-
Fibrous band	-	-	+	-	+	-	+	-	-
Subpleural sparing	-	-	-	+	+	-	-	-	-
Halo sign	-	-	-	-	-	-	-	-	-
Reversed halo sign	-	-	-	-	-	-	-	-	-
Extrapulmonary manifesation									
Pleural thickening	-	+	+	+	-	-	-	-	-
Lymphadenopaty	-	-	-	-	-	-	-	-	-
Pleural effusion	-	-	-	-	-	-	-	-	-
Pneumomediastenum and Pneumothorax	-	-	-	-	-	-	+	-	-
CT: Computed tomography, RT-PCR: Reverse transcription polymerase chain reaction, COVID-19: Coronavirus disease-2019									

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Figure 3. CT images obtained 2 hours after emergency cesarean section due to fetal distress of a 25-year-old woman with COVID-19. Coronal images (a,b) show bilateral diffuse and multiple patchy ground-glass opacities with partial consolidation. CT severity index is 22 and classified as severe. All CT images (a-d) show air in the mediastinum which outlines mediastinal organs (black arrows). Also, axial CT images (c,d) show extensive subcutaneous emphysema (white arrows) in the anterior chest wall

CT: Computed tomography, COVID-19: Coronavirus disease-2019

trimester of pregnancy has been shown to affect the clinical severity of COVID-19 (34). However, in our study, although there is a percentage difference between trimesters, the reason for not having a statistically significant relationship may be the relatively small number of patients. RT-PCR test positivity was not observed in any of the delivered fetuses, which supports the notion that the disease has no vertical transmission (35,36).

Study limitation

The limitations of our study are the absence of multiple RT-PCR tests in some pregnant women and the relatively low number of patients included in the study.

Conclusion

This study describes the main radiological features of symptomatic pregnant women infected with COVID-19. The refusal rate among pregnant women for the imaging modalities involving ionizing radiation was high but both CXR and chest CT had high sensitivity for COVID-19 diagnosis. The preterm birth and cesarean section rates were observed as remarkably increased.

Ethics Committee Approval: *The study was approved by the Ethical Committee of the University of Health Sciences Turkey, Kartal Koşuyolu Training and Research Hospital (approval number: 2020.4/07-312) and the national health authorities.*

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