








RESEARCH ARTICLE

Management of pregnant women with COVID-19: A tertiary pandemic center experience on 1416 cases

Dilek Sahin¹ | Atakan Tanacan²  | Seyit Ahmet Erol²  |
Fatma Didem Yucel Yetiskin² | Berhan Besimoglu² | Eda Ozden Tokalioglu²  |
Ali Taner Anuk²  | Ezgi Turgut² | Sule Goncu Ayhan²  | Batuhan Turgay^{2,3} |
Serpil Unlu⁴ | Gozde Kanmaz⁵ | Bedia Dinc⁶ | A. Seval Ozgu-Erdinc²  |
Huseyin Levent Keskin¹ | Aziz Ahmet Surel⁷ | Ozlem Moraloglu Tekin¹ 

¹Department of Obstetrics and Gynecology, University of Health Sciences, Turkish Ministry of Health, Ankara City Hospital, Ankara, Turkey

²Department of Obstetrics and Gynecology, Turkish Ministry of Health, Ankara City Hospital, Ankara, Turkey

³Department of Obstetrics and Gynecology, Yildirim Beyazıt University, Ankara, Turkey

⁴Department of Infectious Diseases, Turkish Ministry of Health, Ankara City Hospital, Ankara, Turkey

⁵Department of Pediatrics, Division of Neonatology, Turkish Ministry of Health, Ankara City Hospital, Ankara, Turkey

⁶Department of Clinical Microbiology, Ministry of Health Ankara City Hospital, Ankara, Turkey

⁷Department of General Surgery, Coordinator Head Physician of Turkish Ministry of Health, Ankara City Hospital, Ankara, Turkey

Correspondence

Atakan Tanacan, Department of Obstetrics and Gynecology, Turkish Ministry of Health, Ankara City Hospital, Üniversiteler Mahallesi 1604. Cadde No. 9, Ankara 06800, Turkey.
Email: atakantanacan@yahoo.com

Abstract

The aim of this study is to share the comprehensive experience of a tertiary pandemic center on pregnant women with COVID-19 and to compare clinical outcomes between pregnancy trimesters. The present prospective cohort study consisted of pregnant women with COVID-19 who were followed up at Ankara City Hospital between March 11, 2020 and February 20, 2021. Clinical characteristics and perinatal outcomes were compared between the pregnancy trimesters. A total of 1416 pregnant women (1400 singletons and 16 twins) with COVID-19 were evaluated. Twenty-six (1.8%) patients were admitted to the intensive care unit (ICU) and maternal mortality was observed in six (0.4%) cases. Pregnancy complications were present in 227 (16.1%) cases and preterm labor was the most common one ($n = 42$, 2.9%). There were 311, 433, and 672 patients in the first, second, and third trimesters of pregnancy, respectively. Rates of mild and severe/critic COVID-19 were highest in the first and second trimesters, respectively. The hospitalization rate was highest in the third trimester. Pregnancy complications, maternal mortality, and NICU admission rates were similar between the groups. The course of the disease and obstetric outcomes may be different among pregnancy trimesters. A worse course of the disease may be observed even in pregnant women without any coexisting health problems.

KEYWORDS

COVID-19, pregnancy outcomes, pregnancy trimesters, SARS-CoV-2

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected millions of people since the first day of its emergence, putting countries under intense social, economic, and psychological pressure.^{1,2} Healthcare professionals, in particular, have shown great dedication in this

process and have been at the forefront of the fight against the pandemic.³ As in all areas of life, obstetrics practice has been also affected by the pandemic, and problems began to occur in the management of pregnant patients.⁴ As pregnancy is a unique state including significant immunological, circulatory, respiratory, and endocrine changes, the course and impact of COVID-19 on pregnant women have not been completely clarified, yet. On the other hand,

the data in the current literature indicate that the disease may be more severe in pregnant women and may lead to increased obstetric complications.⁵⁻⁸

Our knowledge of the selection of appropriate medications, follow-up of pregnancy, management of severe COVID-19 cases, the timing of delivery, and vertical transmission is still limited.⁹⁻¹² Furthermore, there are few studies investigating the effect of pregnancy trimesters on the clinical course and complications of the disease.¹³⁻¹⁵ For this reason, experiences of pandemic centers dealing with many patients are crucial to provide better healthcare for the patients.

The present study aims to share the comprehensive experience of a tertiary pandemic center on pregnant women with COVID-19 and to compare clinical outcomes of pregnancy trimesters.

2 | MATERIALS AND METHODS

The present prospective cohort study consisted of pregnant women with COVID-19 who were followed up at the Department of Obstetrics and Gynecology, Ankara City Hospital between March 11, 2020 and February 20, 2021. All cases with SARS-CoV-2 ribonucleic acid confirmation by real-time polymerase chain reaction (RT-PCR) on nasopharyngeal and oropharyngeal samples were included. Cases admitted to the hospital with suspected COVID-19 but were found to have other infectious agents as a result of the examinations were excluded from the study. Both the Turkish Ministry of Health and the institutional ethics committee approved the study protocol (E2-21-496). All participants gave written informed consent.

This study is the latest update of the previous two studies by Sahin et al.^{16,17} In the first part of the study, demographic features, clinical characteristics, medications, initial laboratory test results, and perinatal outcomes of all patients were reported. Maternal age, gravidity, parity, living child, previous miscarriage, prepregnancy body mass index (BMI), route of admission to hospital, comorbid diseases, gestational age at diagnosis, pregnancy trimester at diagnosis, initial symptoms, close contact with a confirmed or suspected case, abnormal vital signs at admission to hospital, pregnancy-specific medications, COVID-19 medications, antibiotherapy for other pathogens, respiratory support, intensive care unit (ICU) admission, maternal mortality rate, hospitalization rate, length of hospital stay, complete blood cell count, serum biochemistry values, radiologic imaging, blood groups, pregnancy complications, delivery status, time interval between diagnosis and delivery, route of delivery, cesarean section indications, labor anesthesia, spontaneous labor rate, frequency of preterm deliveries, gestational age at delivery, birth weight, 1st and 5th minute Apgar scores, neonatal intensive care unit (NICU) admission rates and vertical transmission were all recorded. Afterward, maternal mortality cases with COVID-19 were evaluated. Finally, clinical characteristics and perinatal outcomes were compared between the pregnancy trimesters. The management of all cases was performed by a multidisciplinary and highly experienced team considering the current guidelines.^{11,12,18} The severity of COVID-19 was

assessed according to the national guideline.¹⁸ All physical, ultrasonographic examinations and deliveries were performed using necessary personal protective equipment.¹⁹

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS.22, IBM SPSS Statistics for Windows, Version 22.0; IBM Corp.). The normality of distribution was investigated by visual and analytical methods (Shapiro-Wilk's test). Descriptive analyses were presented as means and standard deviations. As continuous variables were normally distributed, the one-way analysis of variance or Student's *t* tests were performed to compare the mean values among the groups. Posthoc analysis with the Tukey test was performed to assess the significance of pairwise differences using the Bonferroni correction to adjust for multiple comparisons. An overall 5% type-I error level was used to infer statistical significance. Categorical data were presented as percentages. Chi-square test was used to compare categorical variables among the groups. A two-tailed $p < 0.05$ was regarded as statistically significant.

3 | RESULTS

A total of 1416 pregnant women (1400 singletons and 16 twins) with COVID-19 were followed up at Ankara City Hospital during the study period. Demographic features and clinical characteristics of all cases were summarized in Table 1. Three hundred and twenty-six (23.1%) patients had comorbid diseases and obesity was the leading health problem with 169 (11.9%) cases. Five hundred and sixty-seven (40.1%) patients were asymptomatic at admission to the hospital. Cough ($n = 392$, 27.7%), myalgia ($n = 350$, 24.7%) and dyspnea ($n = 233$, 16.4%) were the most common initial symptoms. One hundred and eighty-eight (13.3%) patients had close contact with a confirmed or suspected case. Tachycardia ($n = 327$, 23.1%) and fever (body temperature $\geq 38^\circ\text{C}$) ($n = 83$, 13.3%) were the most common abnormal vital signs at admission to hospital. Sixty-seven (4.7%) patients received prophylactic antenatal corticosteroid therapy. Tocolysis was performed in 32 (2.2%) cases. Therapy for COVID-19 was administered in 780 (55.1%) patients. Low-molecular-weight heparin ($n = 723$, 51.1%), hydroxychloroquine ($n = 162$, 11.4%) and systemic corticosteroid ($n = 113$, 7.9%) were the most common medications. Antibiotherapy for other pathogens was applied in 280 (19.7%) cases. There were 1322 (93.4%), 65 (4.6%), 14 (1%), and 15 (1%) patients with mild, moderate, severe, and critical COVID-19, respectively. Respiratory support was necessitated in 103 (7.3%) cases and seven (0.4%) patients were intubated. Twenty-six (1.8%) patients were admitted to ICU and maternal mortality was observed in six (0.4%) cases. Seven hundred and ninety-two patients were hospitalized and the mean length of hospital stay was 3.15 ± 3.76 days.

Initial laboratory test results of pregnant women with COVID-19 is shown in Table 2. One hundred and thirty-seven (9.7%) cases had anemia ($\text{Hb} < 10 \text{ mg/d}$). Lymphocytopenia ($< 1000/\text{mm}^3$ or $< 8\%$ of leukocytes) was observed in 433 (30.6%) cases. Elevated liver enzymes (ALT and AST \geq twice the upper limit) were observed in 66 (4.6%) patients and hypokalemia ($K < 2.5 \text{ mmol/L}$) was present in

TABLE 1 Demographic features and clinical characteristics of pregnant women with COVID-19 (*n* = 1416)

Variables	Values
Maternal age (years) (mean ± SD) (min-max)	28.47 ± 5.63 (17-47)
Gravidity (median) (IQR, min-max)	2 (2, 0-10)
Parity (median) (IQR, min-max)	1 (2, 0-7)
Living child (median) (IQR, min-max)	1 (2, 0-7)
Previous miscarriage (median) (IQR, min-max)	0 (0, 0-6)
Prepregnancy BMI (kg/m ²) (mean ± SD) (min-max)	26.75 ± 5.34 (18-45)
Route of admission to the hospital	
Emergency service (<i>n</i> , %)	681 (48.1%)
Ambulance (<i>n</i> , %)	323 (22.8%)
Referral from another hospital (<i>n</i> , %)	412 (29.1%)
Comorbid disease (<i>n</i> , %)	
Obesity (<i>n</i> , %)	169 (11.9%)
Hypothyroidism (<i>n</i> , %)	72 (5.1%)
Hypertension (<i>n</i> , %)	20 (1.4%)
Asthma (<i>n</i> , %)	19 (1.3%)
Diabetes mellitus type 2 (<i>n</i> , %)	12 (8.5%)
Rheumatological disease (<i>n</i> , %)	10 (0.7%)
Cardiovascular disease (<i>n</i> , %)	8 (0.5%)
Diabetes mellitus type 1 (<i>n</i> , %)	5 (0.3%)
Epilepsy (<i>n</i> , %)	4 (0.3%)
Renal disease (<i>n</i> , %)	3 (0.2%)
ITP (<i>n</i> , %)	2 (0.1%)
Thalassemia minor (<i>n</i> , %)	2 (0.1%)
Gestational age at diagnosis (weeks) (mean ± SD) (min-max)	25.59 ± 11.13 (4-41)
Pregnancy trimester at diagnosis	
First (<i>n</i> , %)	311 (22%)
Second (<i>n</i> , %)	433 (30.6%)
Third (<i>n</i> , %)	672 (47.5%)
Initial symptoms	
Asymptomatic (<i>n</i> , %)	567 (40.1%)
Symptomatic (<i>n</i> , %)	849 (59.9%)
Cough (<i>n</i> , %)	392 (27.7%)
Myalgia (<i>n</i> , %)	350 (24.7%)
Dyspnea (<i>n</i> , %)	233 (16.4%)
Headache (<i>n</i> , %)	127 (8.9%)
Anosmia (<i>n</i> , %)	109 (7.7%)
Sore throat (<i>n</i> , %)	103 (7.3%)

TABLE 1 (Continued)

Variables	Values
Nausea-vomiting (<i>n</i> , %)	103 (7.3%)
Ageusia (<i>n</i> , %)	86 (6.1%)
Fever (<i>n</i> , %)	83 (5.8%)
Nasal congestion (<i>n</i> , %)	79 (5.6%)
Diarrhea (<i>n</i> , %)	53 (3.7%)
Chest pain (<i>n</i> , %)	31 (2.2%)
Close contact with a confirmed or suspected case (<i>n</i> , %)	188 (13.3%)
Abnormal vital signs at admission to hospital	
Tachycardia (heart rate ≥ 100/min) (<i>n</i> , %)	327 (23.1%)
Fever (body temperature ≥ 38°C) (<i>n</i> , %)	83 (13.3%)
Tachypnea (respiratory rate ≥ 20/min) (<i>n</i> , %)	45 (3.2%)
Oxygen saturation ≤ 93% (<i>n</i> , %)	48 (3.4%)
Pregnancy specific medications (<i>n</i> , %)	
Tocolytic agent (<i>n</i> , %)	32 (2.2%)
Antenatal corticosteroid (<i>n</i> , %)	67 (4.7%)
COVID-19 therapy (<i>n</i> , %)	
Low-molecular weight heparin (<i>n</i> , %)	723 (51.1%)
Hydroxychloroquine (<i>n</i> , %)	162 (11.4%)
Systemic corticosteroid (<i>n</i> , %)	113 (7.9%)
Favipiravir (<i>n</i> , %)	82 (5.8%)
Lopinavir-ritonavir (<i>n</i> , %)	78 (5.5%)
Convalescent plasma (<i>n</i> , %)	37 (2.6%)
Azithromycin (<i>n</i> , %)	30 (2.1%)
N-acetylcysteine (<i>n</i> , %)	24 (1.7%)
rHuL-1Ra (<i>n</i> , %)	20 (1.4%)
Colchicine (<i>n</i> , %)	6 (0.4%)
High-dose vitamin C (<i>n</i> , %)	5 (0.3%)
Remdesivir (<i>n</i> , %)	4 (0.3%)
Tocilizumab (<i>n</i> , %)	1 (0.07%)
Dornase alpha (<i>n</i> , %)	1 (0.07%)
Antibiotherapy for other pathogens (<i>n</i> , %)	280 (19.7%)
COVID-19 severity	
Mild (<i>n</i> , %)	1322 (93.4%)
Moderate (<i>n</i> , %)	65 (4.6%)
Severe (<i>n</i> , %)	14 (1%)
Critic (<i>n</i> , %)	15 (1%)
Respiratory support (<i>n</i> , %)	
Nasal oxygen therapy (<i>n</i> , %)	76 (5.4%)

TABLE 1 (Continued)

Variables	Values
High-flow nasal cannula (n, %)	12 (0.8%)
Oxygen mask with reservoir bag	8 (0.5%)
Invasive mechanical ventilation (n, %)	7 (0.4%)
ICU admission (n, %)	26 (1.8%)
Maternal mortality (n, %)	6 (0.4%)
Hospitalization rate (n, %)	792 (55.9%)
Length of hospital stay (mean ± SD) (min-max)	3.15 ± 3.76 (1-35)

Abbreviations: BMI, body-mass index; COVID-19, coronavirus disease 19; ICU, intensive care unit; IQR, inter-quartile range; ITP, immune thrombocytopenic purpura; rHuIL-1Ra, recombinant human IL-1 receptor antagonist; SD, standard deviation.

41 (2.9%) cases. Radiologic imaging was performed in 167 (11.8%) patients and 111 of them were consistent with COVID-19. A Rh+ and 0 Rh+ were the most common blood group types (41.1% and 29.4%, respectively).

Obstetric and neonatal outcomes of pregnant women with COVID-19 are shown in Table 3. Pregnancy complications were present in 227 (16.1%) cases and preterm labor was the most common one ($n = 42$, 2.9%) followed by miscarriage ($n = 29$, 2.1%). A fetal anomaly was observed in 17 (1.2%) fetuses (seven cardiac, five central nervous systems, one nonimmune hydrops fetalis, one unilateral renal agenesis, one skeletal dysplasia, one congenital cataract, and one cleft lip/palate). Eight hundred and fifty-one patients gave birth during the study period and pregnancy loss was observed in 53 (3.7%) cases. Cesarean section was performed in 543 (63.8%) patients and vaginal birth after the cesarean section occurred in three (0.3%) cases. Previous cesarean section was the leading indication ($n = 214$, 39.4%) followed by fetal distress ($n = 154$, 28.4%). General anesthesia was only performed in 24 (2.8%) cases. Spontaneous labor was observed in 719 (84.5%) patients and the preterm delivery rate was 18.8% among the total 851 deliveries. One hundred and seventy-seven (20.8%) neonates were admitted to the neonatal intensive care unit due to prematurity or respiratory problems. The RT-PCR study of nasopharyngeal and oropharyngeal samples obtained from all neonates were negative in the first, third, and fourteenth days of postnatal age. One neonate and one of the breastmilk specimen samples obtained from the mothers were positive for SARS-CoV-2.²⁰ However when the placenta, umbilical cord blood, amniotic fluid, and vaginal secretions of the mother whose neonate was positive were evaluated, all the samples were found to be negative for SARS-CoV-2.

Clinical characteristics of maternal mortality cases with COVID-19 were summarized in Table 4. Only one patient had the comorbid disease (obesity). There were one, two, and three patients in the first, second, and third trimesters, respectively. One patient had severe and the remaining patients had critic COVID-19 at admission. All patients had oxygen saturation $\leq 93\%$ upon admission to the hospital.

All patients received multiple medications for COVID-19. Lymphocytopenia was observed in five cases and high levels of inflammation markers were observed in all of them. Five patients had radiologic imaging findings suspicious for COVID-19. Two pregnancies resulted in spontaneous miscarriage and preterm delivery was present in two cases. All deliveries were performed by cesarean section with regional anesthesia. Three neonates were admitted to the neonatal intensive care unit due to prematurity.

A comparison of clinical characteristics and perinatal outcomes of pregnancy trimesters is shown in Table 5. There were 311, 433, and 672 patients in the first, second, and third trimesters of pregnancy, respectively. The rate of asymptomatic patients was significantly higher in the second trimester compared to the other trimesters. Rates of mild and severe/critic COVID-19 were highest in the first and second trimesters, respectively. The hospitalization rate was highest in the third trimester and the mean length of hospital stay was shortest in the first trimester. The rates of radiologic images consistent with COVID-19 increased significantly with advancing trimesters. Of the patients diagnosed as SARS-CoV-2 positive in the first trimester, 29 (9.3%) resulted in miscarriage and only 85 (27.3%) of them delivered. Cesarean section rate was highest in patients who were diagnosed with COVID-19 in the third trimester. The mean birth weight of the neonates delivered from the mothers diagnosed with COVID-19 in the first trimester was higher than the other neonates. Pregnancy complications, maternal mortality, and NICU admission rates were similar between the groups.

4 | DISCUSSION

Appropriate management of pregnancy during the COVID-19 pandemic is a challenging issue as pregnant women have higher risks for the worse clinical course of the disease and increased rates of pregnancy complications.⁵⁻⁷ There are also controversial issues regarding the efficacy of medications, the optimal route of delivery, the safety of breastfeeding, and the risk of vertical transmission.⁹⁻¹² Moreover, there is not enough information in the literature related to the course and possible adverse effects of COVID-19 in different pregnancy trimesters.¹³⁻¹⁵ Thus, cumulative knowledge of the prognosis and perinatal outcomes of pregnant women with COVID-19 is important to establish better clinical protocols.^{16,17} To the best of our knowledge, the present study is the largest series presented from a single center and is one of the few studies examining pregnancy trimesters.¹³⁻¹⁵

Nearly a quarter of patients had comorbid conditions in the present study and the most common of them was obesity. It has been long known that individuals with chronic diseases have a higher risk for severe illness and mortality.^{21,22} Yet, more than 90% of cases had mild disease and only 2% were admitted to NICU. These findings were most probably due to the younger age of the study population. On the other hand, only one patient had comorbidity among the maternal mortality cases. Therefore, physicians should keep in mind

TABLE 2 Initial laboratory test results of pregnant women with COVID-19 (*n* = 1416)

Variables	Values
Hb (g/dl) (mean ± SD) (min-max)	11.88 ± 1.43 (4.7–16.4)
Hct (%) (mean ± SD) (min-max)	35.98 ± 4.27 (26.2–47.1)
Hb < 10 g/dl (<i>n</i> , %)	137 (9.7%)
Leukocyte (10 ³ /mm ³) (mean ± SD) (min-max)	7412.40 ± 2889.65 (1240–28 510)
Leukocytosis (>11 000/mm ³) (<i>n</i> , %)	145 (10.2%)
Neutrophil (10 ³ /mm ³) (mean ± SD) (min-max)	5476.82 ± 2629.86 (1070–25 430)
Neutrophil percentage (%) (mean ± SD) (min-max)	75.74 ± 10.84 (62–90.8)
Neutrophilia (>7700/mm ³ or >70% of leukocytes) (<i>n</i> , %)	218 (15.4%)
Lymphocyte (10 ³ /mm ³) (mean ± SD) (min-max)	1330.67 ± 576.97 (140–4650)
Lymphocyte percentage (%) (mean ± SD) (min-max)	22.40 ± 9.51 (1.8–51.8)
Lymphocytopenia (<1000/mm ³ or <8% of leukocytes) (<i>n</i> , %)	433 (30.6%)
Neutrophil to lymphocyte ratio (mean ± SD) (min-max)	5.51 ± 3.39 (1.2–25.28)
Platelet (10 ³ /mm ³) (mean ± SD) (min-max)	225 697.74 ± 68 554.55 (19 000–708 000)
ESR (mm/h) (mean ± SD) (min-max)	41.10 ± 23.64 (2–113)
CRP (mg/dl) (mean ± SD) (min-max)	22.78 ± 32.76 (1–419)
Procalcitonin (ng/ml) (mean ± SD) (min-max)	0.16 ± 2.87 (0–96.85)
IL-6 (pg/ml) (mean ± SD) (min-max)	73.15 ± 134.19 (0–22 524)
Ferritin (ng/ml) (mean ± SD) (min-max)	50.04 ± 269.21 (10–9130)
BUN (mmol/L) (mean ± SD) (min-max)	16.68 ± 8.13 (9–75)
Creatinine (mg/dl) (mean ± SD) (min-max)	0.57 ± 2.44 (0.30–4.85)
ALT (IU/L) (mean ± SD) (min-max)	26.12 ± 41.73 (8–884)
AST (IU/L) (mean ± SD) (min-max)	28.10 ± 45.80 (9–1065)
Elevated liver enzymes (<i>n</i> , %) (ALT and AST ≥ twice the upper limit)	66 (4.6%)
LDH (IU/L) (mean ± SD) (min-max)	220.66 ± 138.98 (125–3780)
D-Dimer (mcg/ml) (min-max)	2.08 ± 3.26 (0.01–67.25)
CK-MB (ng/ml) (mean ± SD) (min-max)	1.10 ± 2.32 (0–45.6)
Troponin (ng/ml) (mean ± SD) (min-max)	5.30 ± 77.85 (0–654)
Hypokalemia (<i>K</i> < 2.5 mmol/L) (<i>n</i> , %)	41 (2.9%)
Radiologic imaging (<i>n</i> , %)	167 (11.8%)
Chest X-ray (<i>n</i> , %)	103 (7.3%)

TABLE 2 (Continued)

Variables	Values
Chest CT (<i>n</i> , %)	80 (5.6%)
Pulmoner CT angiography (<i>n</i> , %)	6 (0.4%)
Radiologic imaging findings suspicious for COVID-19 (<i>n</i> , %)	111 (7.8%)
Blood type	
A Rh+ (<i>n</i> , %)	582 (41.1%)
A Rh- (<i>n</i> , %)	66 (4.6%)
B Rh+ (<i>n</i> , %)	182 (12.8%)
B Rh- (<i>n</i> , %)	21 (1.4%)
O Rh+ (<i>n</i> , %)	417 (29.4%)
O Rh- (<i>n</i> , %)	39 (2.7%)
AB Rh+ (<i>n</i> , %)	36 (2.5%)
AB Rh- (<i>n</i> , %)	73 (5.1%)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; COVID-19, coronavirus disease 19; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Hb, hemoglobin; Hct, Hematocrit; IL-6, interleukin 6; IQR, inter-quartile range; LDH, lactate dehydrogenase; SD, standard deviation.

that the worse course of the disease may be observed even in pregnant women without any coexisting health problems.

According to the results of a report including a large population of patients from the United States, approximately 90% of cases were symptomatic at hospital admission. Cough, headache, myalgia, and fever were the most common clinical findings reported in the infected pregnant women.²³ Forty percent of the cases in the present study were asymptomatic. Cough, myalgia, and dyspnea were the most frequent initial symptoms. Although these results were relatively consistent with the literature, the number of asymptomatic cases was higher than the current report most probably due to the high number of screening tests performed by the national filiation teams.²³

Another important topic is the administration of pregnancy-specific medications, International societies recommend the application of routine antenatal medication protocols like tocolysis and antenatal corticosteroids in necessary conditions as far as the patient's condition allows.^{11,12} Tocolytic agents were rarely used in the present study and antenatal corticosteroids were only administered in 5% of the cases.

Specific therapy for COVID-19 was given to more than half of the cases in the present study. Low-molecular-weight heparin, hydroxychloroquine, and systemic corticosteroid were the most common medications. Furthermore, antibiotherapy for other pathogens was administered to approximately 20% of the patients. The safety and efficacy of COVID-19 medications during pregnancy are a matter of debate.^{24,25} However, our individualized approach was provided for all cases and COVID-19 therapy was started as soon as possible in

TABLE 3 Obstetric and neonatal outcomes of pregnant women with COVID-19 (*n* = 1416)

Variables	Values
Pregnancy complications (<i>n</i> , %)	227 (16.1%)
Threatened abortion (<i>n</i> , %)	10 (0.7%)
Miscarriage (<i>n</i> , %)	29 (2.1%)
Hiperemesis Gravidarum (<i>n</i> , %)	10 (0.7%)
Cholestasis of pregnancy (<i>n</i> , %)	13 (0.9%)
Fetal anomaly (<i>n</i> , %) ^a	17 (1.2%)
Intrauterine fetal demise (<i>n</i> , %)	24 (1.7%)
Fetal growth restriction (<i>n</i> , %)	16 (1.1%)
Gestational diabetes (<i>n</i> , %)	20 (1.4%)
Gestational hypertension (<i>n</i> , %)	11 (0.7%)
Preterm labor (<i>n</i> , %)	42 (2.9%)
Preterm premature rupture of the membranes (<i>n</i> , %)	14 (0.9%)
Pre-eclampsia (<i>n</i> , %)	11 (0.7%)
Eclampsia (<i>n</i> , %)	2 (0.1%)
Placental abruption (<i>n</i> , %)	2 (0.1%)
Deep vein thrombosis (<i>n</i> , %)	3 (0.2%)
Clavicle fracture (<i>n</i> , %)	3 (0.2%)
Delivery status	
Pregnancy loss (<i>n</i> , %)	53 (3.7%)
Ongoing pregnancy (<i>n</i> , %)	512 (36.2%)
Delivered (<i>n</i> , %)	851 (60.1%)
The time interval between diagnosis and delivery (days) (mean ± SD) (min–max)	7.82 ± 9.12 (1–34)
Route of delivery	
Normal spontaneous vaginal delivery (<i>n</i> , %)	305 (35.8%)
Cesarean section (<i>n</i> , %)	543 (63.8%)
Vaginal birth after cesarean section (<i>n</i> , %)	3 (0.3%)
Cesarean indications	
Previous cesarean section (<i>n</i> , %)	214 (39.4%)
Fetal distress (<i>n</i> , %)	154 (28.4%)
Cefalopelvic dysproportion (<i>n</i> , %)	96 (17.6%)
Maternal health condition (<i>n</i> , %)	27 (4.9%)
Malpresentation (<i>n</i> , %)	25 (4.6%)
Multiple pregnancy (<i>n</i> , %)	16 (2.9%)
Macrosomia (<i>n</i> , %)	11 (2.1%)
Labor anesthesia	
None (<i>n</i> , %)	308 (36.2%)
General (<i>n</i> , %)	24 (2.8%)
Regional (<i>n</i> , %)	519 (60.9%)
Spontaneous labor (<i>n</i> , %)	719 (84.5%)

(Continues)

TABLE 3 (Continued)

Variables	Values
Preterm delivery (<i>n</i> , %)	160 (18.8%)
Gestational age at delivery (weeks) (mean ± SD) (min–max)	37.82 ± 2.52 (28–42)
Birth weight (g) (mean ± SD) (min–max)	3141.15 ± 617.42 (540–4550)
Apgar 1st minute (median) (IQR, min–max)	8 (1, 6–9)
Apgar 5th minute (median) (IQR, min–max)	9 (1, 8–10)
NICU admission (<i>n</i> , %)	177 (20.8%)
Neonatal SARS-CoV-2 positivity (<i>n</i> , %)	1 (0.2%)
SARS-CoV-2 positivity in the breastmilk	1 (0.2%)

Abbreviations: BMI, body-mass index; COVID-19, coronavirus disease 19; IQR, inter-quartile range; NICU, neonatal intensive care unit; RT-PCR, real-time polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation.

^aSeven cardiac, five central nervous system, one nonimmune hydrops fetalis, one unilateral renal agenesis, one skeletal dysplasia, one congenital cataract, one cleft lip/palate.

necessary situations. The severity of the disease, laboratory parameters, and need for oxygen were all taken into account to choose the most suitable treatment protocol.

The majority of the patients had a mild disease in the present study and only 2% of the cases were severe or critical. Approximately half of the cases were hospitalized. Respiratory support was necessary in 7% of the cases, and most of them received nasal oxygen therapy. ICU admission and maternal mortality rates were similar to the current literature.⁵ Maternal mortality cases in the present study had mostly severe/critical COVID-19 upon admission to the hospital and they had high levels of impaired initial laboratory test results. Thus, physicians should be extremely cautious in the management of pregnant women with severe infection and the possibility of rapid worsening in maternal condition should be kept in mind.

Impaired laboratory test results like lymphocytopenia, elevated liver enzymes, increased levels of ferritin, lactate dehydrogenase, D-dimer, C-reactive protein, and troponin were reported in patients with COVID-19.²⁶ Lymphocytopenia was the most common impaired laboratory finding in the present study. Radiologic imaging of the lungs is important for evaluation in infected individuals.²⁷ However, the use of radiologic imaging in the pregnant population is generally limited mostly due to the anxiety of patients for radiation. For this reason, our knowledge is limited on pregnant women with COVID-19 and some experts recommend the extended use of lung ultrasonography in these patients.^{28,29} Lung ultrasonography could not be performed effectively in our institution, so we preferred conventional imaging modalities. Radiologic imaging could be performed only in 12% of the cases in the present study and chest X-ray was the most common methodology. On the other hand, the majority of the imaging findings were consistent with COVID-19 pneumonia.

TABLE 4 Clinical characteristics of maternal mortality cases with COVID-19 (*n* = 6)

Variables	Values
Maternal age (years) (mean ± SD) (min-max)	30.83 ± 6.82 (22-41)
Primiparous (<i>n</i> , %)	3 (50%)
Multiparous (<i>n</i> , %)	3 (50%)
Comorbid disease (<i>n</i> , %)	1 (16.6%)
Gestational age at diagnosis (weeks) (mean ± SD) (min-max)	27.33 ± 10.48 (12-40)
Pregnancy trimester at diagnosis	
First (<i>n</i> , %)	1 (16.6%)
Second (<i>n</i> , %)	2 (33.3%)
Third (<i>n</i> , %)	3 (50%)
COVID-19 severity	
Mild (<i>n</i> , %)	0 (0%)
Moderate (<i>n</i> , %)	0 (0%)
Severe (<i>n</i> , %)	1 (16.6%)
Critic (<i>n</i> , %)	5 (83.3%)
Abnormal vital signs at admission to hospital	
Tachycardia (heart rate ≥ 100/min) (<i>n</i> , %)	4 (66.6%)
Fever (body temperature ≥ 38°C) (<i>n</i> , %)	2 (33.3%)
Tachypnea (respiratory rate ≥ 20/min) (<i>n</i> , %)	3 (50%)
Oxygen saturation ≤ 93% (<i>n</i> , %)	6 (100%)
Tocolytic agent (<i>n</i> , %)	1 (16.6%)
Antenatal corticosteroid (<i>n</i> , %)	2 (33.3%)
COVID-19 therapy (<i>n</i> , %)	
Low-molecular weight heparin (<i>n</i> , %)	6 (100%)
Hydroxychloroquine (<i>n</i> , %)	2 (33.3%)
Systemic corticosteroid (<i>n</i> , %)	6 (100%)
Favipiravir (<i>n</i> , %)	2 (33.3%)
Lopinavir-ritonavir (<i>n</i> , %)	2 (33.3%)
Convalescent plasma (<i>n</i> , %)	1 (16.6%)
N-acetylcysteine (<i>n</i> , %)	2 (33.3%)
rHuIL-1Ra (<i>n</i> , %)	3 (50%)
High-dose vitamin C (<i>n</i> , %)	2 (33.3%)
Tocilizumab (<i>n</i> , %)	1 (16.6%)
Antibiotherapy for other pathogens (<i>n</i> , %)	6 (100%)
Hb < 10 mg/dl (<i>n</i> , %)	1 (16.6%)
Leukocytosis (>11 000/mm ³) (<i>n</i> , %)	0 (0%)
Neutrophilia (>7700/mm ³ or >70% of leukocytes) (<i>n</i> , %)	3 (100%)

TABLE 4 (Continued)

Variables	Values
Lymphocytopenia (<1000/mm ³ or <8% of leukocytes) (<i>n</i> , %)	5 (83.3%)
Neutrophil to lymphocyte ratio (mean ± SD) (min-max)	14.82 ± 8.52 (5-20.3)
ESR (mm/h) (mean ± SD) (min-max)	49.3 ± 36.35 (20-90)
CRP (mg/dl) (mean ± SD) (min-max)	190.73 ± 79.37 (113-272)
Procalcitonin (ng/ml) (mean ± SD) (min-max)	4.26 ± 5.1 (0.43-10.1)
IL-6 (pg/ml) (mean ± SD) (min-max)	612.1 ± 439.3 (135-1000)
Ferritin (ng/ml) (mean ± SD) (min-max)	3358.2 ± 5015.8 (58-9130)
Elevated liver enzymes (<i>n</i> , %) (ALT and AST ≥ twice the upper limit)	5 (83.3%)
LDH (IU/L) (mean ± SD) (min-max)	816.1 ± 610.3 (389-1515)
D-Dimer (mcg/ml) (min-max)	7.47 ± 4.4 (3.8-12.3)
Troponin (ng/ml) (mean ± SD) (min-max)	195.3 ± 206.2 (0-411)
Hypokalemia (<i>K</i> < 2.5 mmol/L) (<i>n</i> , %)	1 (16.6%)
Radiologic imaging findings suspicious for COVID-19 (<i>n</i> , %)	
Pregnancy complications (<i>n</i> , %)	4 (66.6%)
Miscarriage (<i>n</i> , %)	2 (33.3%)
Preterm labor (<i>n</i> , %)	2 (33.3%)
Delivery status	
Pregnancy loss (<i>n</i> , %)	2 (33.3%)
Delivered (<i>n</i> , %)	4 (66.6%)
Route of delivery	
Normal spontaneous vaginal delivery (<i>n</i> , %)	0 (0%)
Cesarean section (<i>n</i> , %)	4 (100%)
Cesarean indications	
Maternal health condition (<i>n</i> , %)	2 (50%)
Fetal distress (<i>n</i> , %)	2 (50%)
Labor anesthesia	
General (<i>n</i> , %)	0 (0%)
Regional (<i>n</i> , %)	4 (100%)
Spontaneous labor (<i>n</i> , %)	0 (0%)
Gestational age at delivery (weeks) (mean ± SD) (min-max)	33.10 ± 5.1 (28-40)
Birth weight (g) (mean ± SD) (min-max)	17600.20 ± 850.68 (1170-2110)

TABLE 4 (Continued)

Variables	Values
Apgar 1st minute (median) (IQR, min-max)	6 (1, 6-7)
Apgar 5th minute (median) (IQR, min-max)	8 (1, 8-9)
NICU admission (n, %)	3 (75%)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; COVID-19, coronavirus disease 19; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IL-6, interleukin 6; IQR, inter-quartile range; LDH, lactate dehydrogenase; NICU, neonatal intensive care unit; rHuIL-1Ra, recombinant human IL-1 receptor antagonist; SD, standard deviation.

Some studies investigated the relationship between ABO blood types and COVID-19. However, they reported controversial results and the clinical implication of ABO blood types in the management of COVID-19 is not clear.^{30,31} A and O Rh+ were the most common blood types in the present study.

Higher rates of obstetric complications were reported in pregnant women with COVID-19.⁵⁻⁸ Excessive inflammatory response, hypoxia, impaired cytokine production, and coagulation disorders associated with COVID-19 were all considered as the possible pathophysiological events behind poor obstetric outcomes in infected cases.^{32,33} Pregnancy complications were observed in 16% of the cases and preterm labor was the most common one followed by

TABLE 5 Comparison of clinical characteristics and perinatal outcomes between pregnancy trimesters

Variables	First trimester (n = 311)	Second trimester (n = 433)	Third trimester (n = 672)	p value
Asymptomatic (n, %)	141 (45.3%)	118 (27.2%)	308 (45.8%)	<0.001 ^a
Close contact with a confirmed or suspected case (n, %)	32 (10.3%)	62 (14.3%)	94 (13.9%)	0.33
COVID-19 severity				<0.001 ^b
Mild (n, %)	307 (98.8%)	391 (90.3%)	623 (92.7%)	
Moderate (n, %)	2 (0.6%)	25 (5.7%)	38 (5.6%)	
Severe (n, %)	0 (0%)	9 (2.1%)	5 (0.7%)	
Critic (n, %)	2 (0.6%)	6 (1.4%)	7 (1.1%)	
Maternal mortality (n, %)	1 (0.3%)	2 (0.4%)	3 (0.4%)	0.95
Hospitalization rate (n, %)	126 (40.5%)	184 (44.5%)	482 (71.7%)	<0.001 ^c
Length of hospital stay (mean ± SD) (min-max)	1.92 ± 2.66 (1-20)	3.45 ± 4.18 (1-20)	3.14 ± 3.79 (1-35)	<0.001 ^d
Radiologic imaging findings suspicious for COVID-19 (n, %)	3 (0.9%)	25 (5.7%)	83 (12.3%)	<0.001 ^e
Pregnancy complications (n, %)	52 (16.7%)	72 (16.6%)	103 (15.3%)	0.88
Delivery status				
Pregnancy loss (n, %)	29 (9.3%)	20 (4.6%)	4 (0.5%)	<0.001 ^f
Ongoing pregnancy (n, %)	197 (63.3%)	172 (39.7%)	143 (21.3%)	
Delivered (n, %)	85 (27.3%)	241 (55.7%)	525 (78.1%)	
Route of delivery				
Normal spontaneous vaginal delivery (n, %)	40 (47.1%)	103 (42.7%)	174 (33.1%)	<0.001 ^g
Cesarean section (n, %)	45 (52.9%)	136 (56.4%)	350 (66.6%)	
Vaginal birth after cesarean section (n, %)	0 (0%)	2 (0.8%)	1 (0.1%)	
Preterm delivery (n, %)	15 (17.6%)	49 (20.3%)	96 (18.3%)	0.78
Gestational age at delivery (weeks) (mean ± SD) (min-max)	38 ± 2.44 (28-41)	37.6 ± 3.13 (28-42)	37.8 ± 2.13 (29-42)	0.39
Birth weight (g) (mean ± SD) (min-max)	3275.8 ± 519.1 (500-4250)	3070.9 ± 690.3 (540-4500)	3158.6 ± 579.6 (1060-4550)	0.03 ^h
Apgar 1st minute (median) (IQR, min-max)	8 (1, 6-9)	8 (1, 6-9)	8 (1, 6-9)	0.13

(Continues)

TABLE 5 (Continued)

Variables	First trimester (n = 311)	Second trimester (n = 433)	Third trimester (n = 672)	p value
Apgar 5th minute (median) (IQR, min–max)	9 (1, 8–10)	9 (1, 8–10)	9 (1, 8–10)	0.12
NICU admission (n, %)	21 (24.7%)	67 (27.8%)	89 (16.9%)	0.11

Abbreviations: COVID-19, coronavirus disease 19; IQR, inter-quartile range; NICU, neonatal intensive care unit; SD, standard deviation.

^aPairwise comparisons revealed significant differences between first versus second and second versus third trimesters ($p < 0.001$ for both).

^bPairwise comparisons revealed significant differences between first versus second and second versus third trimesters ($p < 0.001$ for both).

^cPairwise comparisons revealed significant differences between first versus third and second versus third trimesters ($p < 0.001$ for both).

^dPairwise comparisons revealed significant differences between first versus second and first versus third trimesters ($p < 0.001$ for both).

^ePairwise comparisons revealed significant differences between first versus second ($p = 0.003$), first versus third (< 0.001), and second versus third trimesters ($p = 0.001$).

^fPairwise comparisons revealed significant differences between first versus second, first versus third, and second versus third trimesters ($p < 0.001$ for all).

^gPairwise comparisons revealed significant differences between first versus second, first versus third, and second versus third trimesters ($p < 0.001$ for all).

^hPairwise comparisons revealed significant differences between first and second trimesters ($p = 0.02$).

miscarriage. Although the effect of COVID-19 on miscarriage has not been identified yet, most of the studies reported increased rates of preterm delivery.^{34,35} Another hot topic in pregnant women with COVID-19 is choosing the optimal route of delivery. Although the cesarean section was the preferred method in the early period of the pandemic, the current trend is to choose the route of delivery according to obstetric indications.^{11,12} Cesarean section was performed in approximately two-thirds of the cases in the present study and previous cesarean section was the most common indication followed by fetal distress. Only 5% of the cesarean section deliveries were performed due to maternal health conditions. These results were consistent with the literature.^{35,36} Regional anesthesia was the preferred method and the majority of the labors had started spontaneously.

Although some studies indicated convincing results for the vertical transmission of COVID-19, no consensus could be reached on this issue.³⁷ One case of neonatal SARS-CoV-2 positivity was observed in the present study and viral RNA was detected only in one breast milk sample.²⁰ Although the NICU admission rate was relatively high, all were due to prematurity or neonatal respiratory distress.

In the present study, the rate of asymptomatic cases was lower, and severe/critical cases were higher in the second trimester compared to the other trimesters. The hospitalization rate was highest in the third trimester, most probably due to the concerns of the physicians. Length of hospital stay was lowest in the first trimester and radiologic imaging findings were highest in the third trimester. In our opinion, high rejection rates for radiologic imaging in the early trimesters might be the reason for these findings. Cesarean section rate was highest in patients diagnosed in the third trimester, most probably due to maternal reasons. Mean birth weight was lowest in the second-trimester cases. However, the mean gestational age at birth was similar between the groups. Maternal mortality, obstetric complication, and NICU admission rates were comparable between the groups.

Although there are studies in the literature focusing on pregnancy trimesters and COVID-19, to the best of our knowledge present study is the most comprehensive research investigating the outcomes of pregnant women diagnosed at different trimesters.^{13–15}

Recent studies underlined the severe course of COVID-19 in pregnant women. Pregnant women with SARS-CoV-2 infection have higher risks for ICU admission, invasive ventilation, and maternal mortality.^{38,39} For this reason, effective clinical management protocols should be established by a multidisciplinary medical team to prevent pregnant women from COVID-19 related fatal complications.⁴⁰ Vaccination of pregnant women against SARS-CoV-2 was reported to be associated with favorable outcomes.^{41,42} Although many pregnant women are still reluctant to get vaccinated, vaccination is an effective and safe protective measure in these special populations.⁴³ Therefore, vaccination should be encouraged by healthcare professionals and immunization programs should be organized by the states.

The main strengths of the present study were the large number of cases, prospective design, and the high number of study parameters. Moreover, a comparison of patients diagnosed at different pregnancy trimesters was the other important part. On the other hand, the lack of information related to the long-term outcomes of the cases was the main limitation.

In conclusion, an individualized approach should be provided to pregnant women with COVID-19, and management of these cases should be performed within the framework of a multidisciplinary team.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

All the authors cited in the manuscript had substantial contributions to the concept and design, the execution of the work, or the analysis and interpretation of data; drafting or revising the manuscript, and have read and approved the final version of the paper. Dilek Sahin: Conceptualization, methodology, visualization, reviewing, and editing. Atakan Tanacan: Original draft preparation, writing, data collection. Seyit Ahmet Erol: Data collection. Fatma Didem Yucel Yetiskin: Data collection. Berhan Besimoglu: Data collection. Eda Ozden Tokalioglu: Data collection. Ali Taner Anuk: Data collection. Ezgi Turgut: Reviewing and editing. Sule Goncu Ayhan: Literature search. Batuhan Turgay: Reviewing and editing. Serpil Unlu: Data collection. Gozde Kanmaz: Data collection. Bedia Dinc: Resources, analysis/interpretation. A. Seval Ozgu-Erdinc: Analysis/interpretation. Huseyin Levent Keskin: Analysis/interpretation. Aziz Ahmet Surel: Supervision. Ozlem Moraloglu Tekin: Project development.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Atakan Tanacan  <http://orcid.org/0000-0001-8209-8248>

Seyit Ahmet Erol  <http://orcid.org/0000-0002-2494-4896>

Eda Ozden Tokalioglu  <http://orcid.org/0000-0003-4901-0544>

Ali Taner Anuk  <http://orcid.org/0000-0001-5437-1008>

Sule Goncu Ayhan  <http://orcid.org/0000-0002-5770-7555>

A. Seval Ozgu-Erdinc  <http://orcid.org/0000-0002-6132-5779>

Ozlem Moraloglu Tekin  <http://orcid.org/0000-0001-8167-3837>

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