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A cross-sectional evaluation of maternal and perinatal outcomes in pregnancies complicated with COVID-19

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Abstract

Aim: Pregnancy is considered a vulnerable period for women regarding increased risk of respiratory tract infections, altered immunity, and metabolic changes in their bodies. COVID-19 pandemic also possesses a significant risk on pregnant women, but the data on the disease course is insufficient. Therefore, this study aimed to evaluate the maternal and perinatal outcomes in pregnant women diagnosed with COVID-19.

Materials and Methods: This cross-sectional study retrospectively evaluated the hospital records of pregnant women admitted to the Obstetrics and Gynecology Department of 19 MayısUniversity Hospital between 01/04/2020 to 30/12/2021 regarding gestational week at birth, basal gestational, and labor characteristics, delivery complications, and perinatal and maternal COVID-19 outcomes.

Results: Analyses of the data of 98 patients revealed that the median age of the mothers was 30 years; 26.5% were primigravid, 43.9% were nulliparous, 29.6% were primiparous, and 3 had twin pregnancies. In addition, 52% of the births were preterm, 88% were cephalic presentation, and 95.9% were cesarean deliveries. The most common delivery complications were acute fetal distress (51%), preterm premature rupture of membranes (50%), and neonatal asphyxia (49%). Gestational characteristics were similar between treatment groups for COVID-19, but patients admitted to intensive care unit and applied mechanical ventilation (11.2%) had significantly more preterm births, and perinatal complications including acute fetal distress (p=0.030), PPROM (p<0.001), neonatal asphyxia (p=0.021), and lower APGAR scores (p=0.002).

Conclusion: COVID-19 is a significant risk factor for pregnant women. This study showed that COVID-19 and pregnancy might induce adverse effects on each other. The data provided here will contribute to the growing epidemiological and clinical evidence on the interactions between COVID-19 and pregnancies.

Introduction

The novel coronavirus disease 2019 (COVID-19), caused by a new type of coronavirus (severe acute respiratory syndrome coronavirus 2 – SARS-CoV-2), is currently the most significant public health emergency in the 21stcentury. Since the World Health Organization (WHO) announced the rapid global spread of the disease as a pandemic on March 11th, 2020, the number of confirmed cases reached 326 million, including more than 5.5 million deaths, as of January 15th, 2022 [1]. The accumulating evidence in the literature suggests that males, individuals over 50 years of age, and patients with several comorbidities, including diabetes, cardiovascular disorders, or hypertension, form the high-risk group for COVID-19 [2].

The pregnancy period is associated with physiological changes in the female body, including respiratory, immune, and cardiovascular adaptations that increase women's susceptibility to severe infections due to decreased immune response to protect the offspring or decreased functional residual capacity [3-5]. However, the studies on the pregnancy outcomes in SARS-CoV-2 infections reported discrepant results, some suggesting increased obstetric complications, but some not [6, 7].

Despite the defined vulnerable groups of patients with comorbidities during the COVID-19 pandemic, the data on the risk classification of pregnant women is scarce [8]. However, pregnancy might be regarded as a risk factor regarding the data reported during the previous severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) epidemics [9, 10].

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There is a paucity of studies about the effects of COVID-19 on pregnancies. However, evaluating the prognosis of pregnant women with COVID-19 is essential to identify the background of disease progression and associated management strategies in this population. Therefore, the primary aim of this study is to evaluate the general characteristics and outcomes of pregnant women with COVID-19.

Materials and Methods

This cross-sectional chart-review study is a retrospective analysis of our case series of COVID-19 positive pregnant women admitted at active labor to the Obstetric and Gynecology Department of the 19 Mayıs University Hospital between 15/04/2020 to 31/12/2021. The data of 98 women were included in the analyses, basal demographic and obstetric characteristics, and the COVID-19 associated characteristics were evaluated comparatively between the gestational and clinical subgroups.

The gestational weeks at delivery were categorized according to the definitions of the World Health Organization, the American College of Obstetricians and Gynecologists, and the Society for Maternal-Fetal Medicine. Accordingly, the preterm births were defined as *extremely preterm* if the gestational week is less than 28 weeks, *very preterm* if $28^{0/7}$to $31^{6/7}$weeks, and *moderate to late preterm* if $32^{0/7}$to $36^{6/7}$weeks [11]. The term births were defined as an *early term* if the gestational week is $37^{0/7}$through $38^{6/7}$, *fullterm* if $39^{0/7}$to $40^{6/7}$, *lateterm* if $41^{0/7}$to $41^{6/7}$, and *postterm* if $42^{0/7}$ weeks and beyond [12].

The COVID-19 was diagnosed or confirmed by polymerase-chain-reaction (PCR) analyses from the nasopharyngeal and throat swabs in our hospital's Microbiology and Infectious Diseases Laboratories. All patients received steroid and low molecular weight heparin to manage COVID-19, and some received additional antiviral medication. The outcomes were categorized as having only pneumonia or being hospitalized in the intensive care unit (ICU) and administered mechanical ventilation (MV) support.

The data analyzed in the study were obtained from electronic patient records or departmental archives.

The study protocol was reviewed and approved by the local ethical committee of the Ondokuz Mayis University Faculty of Medicine on 2021000623-1 and approval number of 2021/623.

Statistical analysis

Descriptive statistics were presented using frequency and percent for categorical variables and median and interquartile range (25th-75th percentiles – IQR) for continuous variables after controlling for normal distribution assumptions. The comparisons between two independent groups were performed using the Chi-square test or Mann-Whitney U test. The comparison between three independent groups was conducted using the Chi-square test and Kruskal-Wallis test. A type-I error level of 5% was considered the threshold of statistical significance in two-tailed hypothesis testings. All analyses were performed in SPSS 25 (IBM Inc., Armonk, NY, USA).

Results

A total of 98 patients were included in the analyses. The median age of the mothers was 30 years; 26.5% were primigravid, 43.9% were nulliparous, and 29.6% were primiparous. One hundred one babies, with a median weight of 2830 grams and 52.5% of males, were born, including three twin pregnancies. All patients were treated using steroids and low molecular weight heparin (LMWH) for COVID, and 18.4% also received antiviral therapies. About 88.8% of cases had only pneumonia, but 11.2% were hospitalized for mechanical ventilation support in the intensive care unit (Table 1).

The gestational characteristics are presented in Table 2. Accordingly, 52% of the births were preterm, 88% were cephalic presentation, and 95.9% were cesarean deliveries. In addition, one baby with the breech presentation was delivered along with hysterectomy, and one with the transverse presentation was delivered by cesarean. The most common delivery complications were acute fetal distress (51%), preterm premature rupture of membranes (PPROM) (50%), and neonatal asphyxia (49%).In addition, patients most commonly underwent cesarean due to recurrent cesarean (37.8%), tube ligation (11.2%), and cephalopelvic disproportion (CPD) (9.2%). The APGAR assessments revealed that 7.1% of babies had scores of

Table 1. General characteristics of the patients.

Mother characteristics	Median [IQR] / n (%)
Age, years	30 [26.3 - 33]
Gravida	2 [1 - 8]
Para	1 [0 - 4]
Abortus	0 [0 - 5]
Alive child	1 [0 - 3]
Gravidity	
Primigravida	26 (26.5)
Multigravida	72 (73.5)
Parity	
Nulliparous	43 (43.9)
Primigravida	29 (29.6)
Multigravida	26 (26.5)
Offspring characteristics	
Weight (gr)	2830 [2250 - 3150]
Sex	
Male	53 (52.5)
Female	48 (475)
COVID status in mothers	
Treatment	
Steroid+LMWH	80 (81.6)
Steroid+ LMWH+Antiviral	18 (18.4)
Status	
Pneumonia	87 (88.8)
ICU+MV	11 (11.2)

Table 2. Gestational characteristics.

		Date of delivery			Gravidity			Parity			
	All patients n (%)	Preterm n (%)	Term n (%)	p	Primigravida n (%)	Multigravida n (%)	p	Nulliparous n (%)	Primiparous n (%)	Multiparous n (%)	p
Delivery week											
Extremely preterm	7 (7.1)	-	-	-	3 (11.5)	4 (5.6)	0.63	4 (9.3)	3 (10.3)	-	0.12
Very preterm	9 (9.2)	-	-		1 (3.8)	8 (11.1)		3 (7)	4 (13.8)	2 (7.7)	
Moderate to late preterm	35 (35.7)	-	-		11 (42.3)	24 (33.3)		21 (48.8)	7 (24.1)	7 (26.9)	
Early term	41 (41.8)	-	-		10 (38.5)	31 (43.1)		12 (27.9)	13 (44.8)	16 (61.5)	
Full term	6 (6.1)	-	-		1 (3.8)	5 (6.9)		3 (7)	2 (6.9)	1 (3.8)	
Delivery presentation											
Cephalic	87 (88.8)	45 (88.2)	42 (89.4)	0.59	21 (80.8)	66 (91.7)	0.21	37 (86)	26 (89.7)	24 (92.3)	0.59
Breech	10 (10.2)	6 (11.8)	4 (8.5)		5 (19.2)	5 (6.9)		6 (14)	2 (6.9)	2 (7.7)	
Transverse	1 (1.0)	-	1 (2.1)		-	1 (1.4)		-	1 (3.4)	-	
Delivery type											
Cesarean	94 (95.9)	49 (96.1)	45 (95.7)	0.004	25 (96.2)	69 (95.8)	0.16	42 (97.7)	26 (89.7)	26 (100)	0.042
Vaginal	3 (3.1)	1 (2)	2 (4.3)		-	3 (4.2)		-	3 (10.3)	-	
Hysterectomy	1 (1.0)	1 (2)	-		1 (3.8)	-		1 (2.3)	-	-	
Delivery complications											
Acute fetal distress	50 (51.0)	36 (70.6)	14 (29.8)	<0.001	13 (50)	37 (51.4)	0.90	26 (60.5)	14 (48.3)	10 (38.5)	0.20
Preterm premature rupture of membranes	49 (50.0)	49 (96.1)	-	<0.001	15 (57.7)	34 (47.2)	0.36	27 (62.8)	13 (44.8)	9 (34.6)	0.061
Neonatal asphyxia	48 (49.0)	38 (74.5)	10 (21.3)	<0.001	14 (53.8)	34 (47.2)	0.56	25 (58.1)	14 (48.3)	9 (34.6)	0.17
Preeclampsia	5 (5.1)	4 (7.8)	1 (2.1)	0.006	2 (7.7)	3 (4.2)	0.61	3 (7)	2 (6.9)	-	0.51
Intrauterine growth restriction	4 (4.1)	2 (3.9)	2 (4.3)	0.010	1 (3.8)	3 (4.2)	1	4 (9.3)	-	-	0.12
Stillbirth	2 (2.0)	2 (3.9)	-	0.008	1 (3.8)	1 (1.4)	0.46	2 (4.7)	-	-	0.50
Cesarean indications											
Recurrent C/S	37 (37.8 %)	14 (27.5)	23 (48.9)	0.017	-	37 (51.4)	<0.001	2 (4.7)	17 (58.6)	18 (69.2)	<0.001
Tube ligation request/indication	11 (11.2 %)	6 (11.8)	5 (10.6)	0.98	2 (7.7)	9 (12.5)	0.72	3 (7)	1 (3.4)	7 (26.9)	0.020
Cephalo-pelvic disproportion	9 (9.2 %)	3 (5.9)	6 (12.8)	0.18	4 (15.4)	5 (6.9)	0.24	6 (14)	2 (6.9)	1 (3.8)	0.41
Placenta decollement	4 (4.1 %)	4 (7.8)	-	0.001	1 (3.8)	3 (4.2)	1	2 (4.7)	2 (6.9)	0 (0)	0.57
Placenta previa	3 (3.1 %)	1 (2)	2 (4.3)	1.0	1 (3.8)	2 (2.8)	1	1 (2.3)	0 (0)	2 (7.7)	0.35
Amniotic fluid disorder	3 (3.1 %)	2 (3.9)	1 (2.1)	0.81	0 (0)	3 (4.2)	0.56	1 (2.3)	0 (0)	2 (7.7)	0.35
APGAR											
0-3	4 (7.1)	3 (9.7)	1 (3.9)	0.006	1 (5.9)	3 (7.5)	0.05	3 (10.7)	0 (0)	1 (7.1)	0.31
4-6	18 (31.6)	13 (41.9)	5 (19.2)		9 (52.9)	9 (22.5)		9 (32.1)	7 (46.7)	2 (14.3)	
7-10	35 (61.4)	15 (48.4)	20 (76.9)		7 (41.2)	28 (70)		16 (57.1)	8 (53.3)	11 (78.6)	

0-3, 31.6% had 4-6, and 61.4% had 7-10. Comparisons between preterm and term births revealed that the cesarean deliveries were less and vaginal deliveries were more in term births (p=0.004), delivery complications (p<0.05) and placenta decollement (p=0.001) were more observed in preterm births, and APGAR scores were higher (p=0.006) in term deliveries. Likewise, higher APGAR scores were observed among babies of multigravida mothers (p=0.05). Comparisons between parity groups showed that cesareans were more prevalent among multiparous mothers, whereas vaginal delivery was observed more in primiparous women (p=0.042). Moreover, the recurrent cesarean indications (p<0.001) and tube ligation (p=0.020) were more prevalent among multiparous women.

Comparing gestational characteristics between treatment groups for COVID revealed no statistically significant difference between patients who received or did not the antiviral therapies along with steroids and LMWH. However,

Table 3. Gestational characteristics according to COVID treatment and outcomes.

	Treatment for COVID			COVID status		
	Steroid+LMWH n (%)	Steroid+LMWH+Antiviral n (%)	p	Pneumonia n (%)	ICU+MV n (%)	p
Delivery week						
Extremely preterm	7 (8.8)	-		3 (42.9)		
Very preterm	8 (10.0)	1 (5.6)		4 (44.4)	4 (57.1)	
Moderate to late preterm	29 (36.3)	6 (33.3)	0.39	33 (94.3)	5 (55.6)	<0.001
Early term	30 (37.5)	11 (61.1)		41 (100)	2 (5.7)	
Full term	6 (7.5)	-		6 (100)	-	
Delivery presentation					-	
Cephalic	73 (91.3)	14 (77.8)		79 (90.8)	8 (72.7)	
Breech	6 (7.5)	4 (22.2)	0.13	7 (8)	3 (27.3)	0.19
Transverse	1 (1.3)	-		1 (1.1)	-	
Delivery type						
Cesarean	76 (95)	18 (100)		84 (96.6)	10 (90.9)	
Vaginal	3 (3.8)	-	1	3 (3.4)	-	0.14
Hysterectomy	1 (1.3)	-		-	1 (9.1)	
Delivery complications						
Acute fetal distress	43 (53.8)	7 (38.9)	0.25	41 (47.1)	9 (81.8)	0.030
Preterm premature rupture of membranes	43 (53.8)	6 (33.3)	0.12	38 (43.7)	11 (100)	<0.001
Neonatal asphyxia	40 (50)	8 (44.4)	0.67	39 (44.8)	9 (81.8)	0.021
Preeclampsia	4 (5)	1 (5.6)	0.92	4 (4.6)	1 (9.1)	0.46
Intrauterine growth restriction	4 (5)	-	1.0	4 (4.6)	-	1.0
Stillbirth	2 (2.5)	-	1.0	1 (1.1)	1 (9.1)	0.21
Cesarean indications						
Recurrent C/S	30 (37.5)	7 (38.9)	0.91	34 (39.1)	3 (27.3)	0.53
Tube ligation request/indication	8 (10)	3 (16.7)	0.42	11 (12.6)	-	0.36
Cephalo-pelvic disproportion	6 (7.5)	3 (16.7)	0.36	8 (9.2)	1 (9.1)	1.0
Placenta decollement	3 (3.8)	1 (5.6)	0.56	2 (2.3)	2 (18.2)	0.061
Placenta previa	1 (1.3)	2 (11.1)	0.086	3 (3.4)	-	1.0
Amniotic fluid disorder	2 (2.5)	1 (5.6)	0.46	3 (3.4)	-	1.0
APGAR						
0-3	3 (6.5)	1 (9.1)		3 (5.9)		
4-6	15 (32.6)	3 (27.3)		13 (25.5)	1 (16.7)	0.002
7-10	28 (60.9)	7 (63.6)		35 (68.6)	5 (83.3)	

the comparisons between patients with only pneumonia and patients hospitalized in the ICU and applied mechanical ventilation showed that the extremely preterm and very preterm births were significantly more prevalent among hospitalized patients ($p<0.001$). In addition, the acute fetal distress ($p=0.030$), PPROM ($p<0.001$), neonatal asphyxia ($p=0.021$), and lower APGAR scores ($p=0.002$) were also more frequent in this group of patients (Table 3).

The CBC and biochemistry assessments and the percent changes in gestational and COVID treatment and status subgroups are presented as Supplementary Tables (Table S1-S2-S3). The comparisons between preoperative and postoperative laboratory analyses showed that hemoglobin ($p<0.001$), C-reactive protein ($p<0.001$), D-dimer ($p<0.001$), direct bilirubin ($p=0.001$), and calcium ($p<0.001$) levels were significantly decreased, whereas the monocyte percent ($p<0.001$), aspartate aminotransferase ($p=0.046$), and sodium ($p<0.001$) levels were significantly increased in the postoperative period (Table S1). In addition, the comparisons between gestational subgroups showed that monocytes ($p=0.014$) and creatinine ($p=0.041$) increased more in preterm pregnancies; sodium ($p=0.010$), potassium ($p=0.032$), and chloride ($p=0.003$) levels increased more in the primigravida group; and aspartate aminotransferase ($p=0.003$), and potassium ($p=0.022$) levels increased more in multiparous pregnancies (Table S2). The significant changes in laboratory parameters were more prominent among patients who received additional antiviral therapy, were hospitalized in the ICU, and needed MV (Table S3).

Discussion

Numerous intrinsic and extrinsic factors may complicate pregnancy, and the recent COVID-19 pandemic can pose a significant risk to pregnant women. This study evaluated the general characteristics and gestational and clinical outcomes in a large sample of COVID-19 positive pregnant women in a tertiary-carehealthcare facility. To summarize, we found that 52.1% of deliveries were preterm, 11.2% were extra-cephalic presentation, and 95.9% undergone cesarean, half of them complicated with acute fetal distress, PPROM, and neonatal asphyxia, one-fifth of cesareans were due to labor emergencies,including CPD, placenta decollement, placenta previa, and amniotic fluid disorder, and about 40% of babies had APGAR scores below 7 at birth. About 20% of mothers received additional antiviral therapies along with steroids and LMWH, and 10% needed ICU and MV. The delivery complications and cesarean rates were higher in preterm births, and lower APGAR scores were more associated with preterm births and primigravida. The proportions of extremely and very preterm births, delivery complications, and lower APGAR scores were higher among patients hospitalized in the ICU, which suggested an association between the severity of COVID-19 and adverse pregnancy outcomes.

The pregnancy itself is considered to increase the adverse outcomes in COVID-19. A study from our country by Tug et al. [13] comparatively evaluated the pregnancy outcomes and clinical characteristics of 188 pregnant women with 799 age-matched non-pregnant women and reported that the clinical severity of COVID-19 worsens especially among pregnants at >20 weeks of gestation, indicated by the significantly increased rates of need for oxygen support, ICU admission, and pregnancy outcomes such as increased cesarean and preterm deliveries. The reverse association is also possible regarding the increased adverse pregnancy outcomes in coronavirus infections. The similarities between the SARS-CoV-2 and the previous SARS- and MERS-associated coronaviruses also suggest similarities in the prognoses. These SARS- and MERS-associated coronaviruses do not cause teratogenic results but may cause significant adverse maternal and fetal outcomes such as abortus, preterm labor, ICU stays, MV, renal failure and dialysis, and disseminated intravascular coagulation [14].

Several studies were published during the pandemic about the effects of COVID-19 on pregnancies. Accordingly, COVID-19 is associated with increased labor complications; however, vertical transmission and teratogenicity data are contradictory. Zhu et al. [15] retrospectively evaluated deliveriesof mothers with COVID-19 and reported that higher rates of fetal distress, preterm labor, respiratory problems, thrombocytopenia, abnormal liver functions, and perinatal mortality might be associated with COVID-19, but no evidence of vertical transmission. Another study by Liu et al. [16] evaluated the perinatal consequences in offsprings of COVID-19 positive mothers and reported that no evidence of vertical transmission or increased perinatal comorbidities were found in babies, but emphasized the importance of complete isolation during labor and immediate separation of babies from mother and caregivers after birth. Another study supporting rapid separation was by Yang et al. [17], which reported that COVID-19 in late pregnancy is not associated with adverse perinatal outcomes, but newborns should be immediately isolated from infected mothers. Despite the lack of evidence regarding vertical transmission in these studies, a large-scale multicenter study from our country by Oncel et al.[18] evaluated the epidemiological and clinical characteristics of 125 newborns of COVID-19 positive mothers and reported significant maternal and neonatal outcomes, including increased preterm and cesarean deliveries and maternal mortality, and suspected risk of vertical transmission.

When our results are compared to studies from other populations and our country, the increased rates of adverse outcomes like preterm births, delivery complications, and lower APGAR scores follow available literature data. Nevertheless, since we did not collect data on the fetal COVID-19 status, we did not analyze the vertical transmission of SARS-CoV-2 from the mother to the fetus. The available data should contribute to the accumulating evidence but need to be confirmed by further epidemiological and clinical studies on larger samples to increase the validity and generalizability. Because, as the understanding of the COVID-19 in pregnancy advances, the study designs also evolve to capture the most accurate evidence, sometimes invalidating the previous ones. For example, our results and several previous studies suggest that preterm labor becomes more frequent as patients are diagnosed with COVID-19 or the severity of COVID-19 increases [19]. However, observational studies from Ireland and Denmark contradictorily suggest that preterm births were dramatically decreased during the pandemic, which is a striking finding that needs to be elucidated [20, 21]. It is also worth mentioning that the novel variants identified in the SARS-CoV-2 might change the clinical course of COVID-19 in pregnancy, and we believe that prospective registries or surveillance systems should be established to monitor the alterations in this vulnerable group.

Besides the valuable data this study provided, there are also some limitations. First, it is a cross-sectional study reflecting the period that data recorded and may not wholly represent the changing landscape in the disease characteristics. Second, although the study was conducted in a tertiary-care healthcare center accepting patients from a large region, it presents a single-center experience. Third, it only included a selected patient population and lacked comparative analyses with a control group of pregnant women without COVID-19 diagnosis. Nevertheless, the results presented will inform both epidemiological and clinical studies with recent data from our population.

Conclusion

COVID-19 pandemic is a significant risk factor per se on the vulnerable or high-risk individuals, including pregnant women. Therefore, identifying epidemiological and clinical characteristics of the disease in this group is essential for enhancing the knowledge for better patient management and maintaining healthy pregnancy, labor, delivery, and maternal and perinatal outcomes. Our results suggest that COVID-19 and pregnancy may induce adverse effects on each other; thus, close follow-up is essential for these

patients.

Supplementary materials

Supplementary tables related to this article are available here online version at doi: http://doi.org/10.5455/annalsmedres.2022.03.080.

Ethics approval

The study protocol was reviewed and approved by the local ethical committee of the Ondokuz Mayis University Faculty of Medicine on 2021000623-1 and approval number of 2021/623.

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