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ORIGINAL ARTICLE

Comparison of maternal and perinatal outcome in pregnant women of SARS-CoV-2 infection in the pandemic

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ABSTRACT

Objective: The coronavirus-2019 pandemic has led to the deaths of many people in the world. Due to the changing physiology in pregnant patients, there is no consensus on the management of the disease. The effects of the disease have decreased over time with the changing virus variants and the spread of the vaccine during the pandemic.

Material and Methods: 231 pregnant patients hospitalized and treated in our clinic due to severe acute respiratory syndrome coronavirus 2 infection between April 2020 and April 2022 were retrospectively analyzed.

Results: Patients were divided into three groups according to the time of occurrence of possible variants. Group 11 (n=99) includes patients with pre-delta, group 2 (n=79) delta, and group 3 (n=53) omicron variants. Considering the vaccine distribution, there is no vaccinated individual in group 1. Individuals in group 2 who are vaccinated in 2 doses have the highest percentage as 42% and group 3 has the highest percentage as 66% ($p<0.01$). Steroid administration to improve respiratory parameters was mostly preferred in patients in groups 1 and 2 (78–57%) ($p=0.022$). O_2 support was found to be statistically significantly higher in groups 1 and 2 compared to group 3. The number of patients who needed O_2 support was found to be lower in group 3 than in the other groups. There was no significant difference between the groups in terms of maternal mortality and morbidity, delivery type, or caesarean section indications. When the length of hospital stay was compared, it was found to be the lowest in group 3 ($p<0.001$). Fetuses in group 3 had the least need for a neonatal intensive care unit.

Conclusion: We think that the management of infectious respiratory diseases during pregnancy should be with a multidisciplinary and holistic perspective. More scientific studies should be conducted on the management of pregnant patients against the potential danger of a new pandemic.

Keywords: Coronavirus-2019, pregnancy, severe acute respiratory syndrome coronavirus 2, vaccination.

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INTRODUCTION

Coronaviruses are enveloped single-stranded RNA viruses in the family Coronaviridea. These infections have caused two epidemic infectious respiratory diseases in the last 20 years, namely the severe acute respiratory syndrome and the Middle East respiratory syndrome.[1] Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pneumonia, which was accepted as an epidemic on December 31, 2020, caused many mortality and morbidities.[2] This severe disease caused by SARS-CoV-2, named as coronavirus-2019 (COVID-19) on February 12, 2020, affected more than 600 million people in the world and caused the deaths of approximately 6 million people.[3] It has been reported that the virus has been detected in 17 million people since March 2020, when it started to show its effect in our country, and approximately 101 thousand people died.[3] Although it varies in many sources, approximately 74–86% of infected pregnant women are asymptomatic.[4] In studies conducted during the pandemic period, it was observed that the symptoms in pregnant women were similar to those of non-pregnant women.[5] Physiological changes during pregnancy probably adversely affect the clinical course of the infection.[6] Studies show that pregnancy does not increase susceptibility to COVID-19 pneumonia, but pregnancy worsens the clinical course of the disease.[7] Pregnant women with COVID-19 have a higher risk of serious illness, the need for mechanical ventilation, intensive care unit (ICU) admission, and maternal death.[8] In addition, higher rates of obstetric complications such as preterm labor, premature rupture of membranes, preterm premature rupture of membranes, fetal distress are observed in pregnancies complicated by COVID-19.[9] In the later stages of the pandemic, the effect of the vaccine on immunity and the effects of the disease are gradually decreasing with the changing variants of the virus.[10] With effective health policies, lifestyle changes, legal regulations, and widespread vaccination programs, significant progress has been made and the effects of the epidemic have decreased.[11] However, since pregnancy changes normal physiology, there is no consensus on the management of pregnant patients in emergency pandemic processes such as epidemics.

In this study, we divided the disease into episodes and evaluated the clinical course of the disease over time, with the mutation effect of the virus and the spread of the vaccine. Thus, we aimed to contribute to the literature on the changing physiology of pregnancy and the management of pregnant patients with infectious respiratory diseases.

MATERIAL AND METHODS

Pregnant patients between the ages of 18 and 40 who were hospitalized due to COVID-19 infection in Istanbul Medeniyet University Prof. Dr. Süleyman Yalçın City Hospital between April 2020 and April 2022 were retrospectively screened. The study was conducted in accordance with the Declaration of Helsinki. Ethics committee approval was obtained from the ethics committee unit of our hospital (2022/0185). Clinical and demographic data were extracted from electronic medical records. All patients were diagnosed with COVID-19 infection by taking a nasopharyngeal swab with reverse transcriptase-polymerase chain reaction (RT-PCR). Patients under the age of 18, pregnant women without RT-PCR, patients with an unconfirmed COVID-19 infection, and patients diagnosed after delivery were excluded from the study. Participants were divided into three groups. Group 1 consists of possible pre-delta variant patients between April 1, 2020, and June 8, 2021, of the pandemic that started with the COVID-19 infection in our country. The patients in Group 2 probable delta variant (June 9, 2021–December 27, 2021) and Group 3 probable omicron (December 27, 2022–April 1, 2022) consist of patients treated with changing treatment regimens and the spread of the vaccine. This grouping was made according to official sources describing the periods when delta and omicron variants were commonly detected in our country.[12]

Data from 3 groups were compared and analyzed in terms of clinical profile, laboratory parameters, maternal, fetal, perinatal, and neonatal outcomes.

All patients were managed according to standard obstetric guidelines.

Statistical Analysis

It was done in the SPSS 22.0 statistical package program. For statistical analysis, categorical variables were presented as numbers, percentages, and continuous variables as mean and standard deviation in the descriptive findings section. Pearson Chi-square test for comparison of categorical variables; the compatibility of the data with the normal distribution was examined with the Kolmogorov-Smirnov test in the comparison of the variables specified by the measurement; and the Kruskal-Wallis test was used to compare three independent groups that were suitable for the normal distribution. Bonferroni corrected Mann–Whitney U Test was used to find which group caused the difference in more than two independent groups. A binary logistic regression analysis of the factors affecting O_2 requirement and neonatal ICU was performed. The statistical significance level was taken as $p<0.05$ in the analysis.

RESULTS

There are 99, 79, and 53 patients in groups 1, 2, and 3, respectively. The comparison of demographic and clinical characteristics between the groups is summarized in Table 1. The demographic results were statistically similar between the groups. The smoking rate of the patients during pregnancy was questioned and it was found to be statistically significant and higher, with a rate of 15% in group 3. Considering the distribution of vaccines between the groups, there were no vaccinated individuals in group 1, 42% of individuals in group 2 who were fully vaccinated in 2 doses, and 66% in group 3. The vaccination rate was highest in group 3 with 54% ($p<0.01$).

Table 2 shows that the rate of antibiotics given to the patients to protect them from secondary bacterial infections was found to be 41%, the highest in group 1, and 90% in group 3 ($p<0.01$). The use of steroids to improve respiratory parameters (prednisolone 2*40 mg 3 days) was mostly preferred in patients in groups 1 and 2 (78–57%) ($p=0.022$). Antenatal corticosteroid (betamethasone 1*12 mg 2 days) groups 1 and 2 were also applied significantly higher. The use of anticoagulation was applied to all patients in group 3 and has the highest rate of use. There was no significant difference between the groups in terms of going to the maternal ICU. However, O_2 support

Table 1: Comparison of demographic and clinical characteristics between the groups

	1 (n=99)	2 (n=79)	3 (n=53)	p
Age				
Mean±SD	31.2±5.7	30.5±6.1	29.5±5.6	0.221
<25	13 (13.1)	16 (20.3)	12 (22.6)	
≥25 and <38	70 (70.7)	53 (67.1)	35 (66.0)	0.553
≥38	16 (16.2)	10 (12.7)	6 (11.3)	
Maternal BMI (kg/m^2)				
Mean±SD	29.9±3.5	29.3±3.4	29.6±3.3	0.660
<25	3 (3.0)	5 (6.3)	2 (3.8)	
25–<30	52 (52.5)	40 (50.6)	27 (50.9)	0.873
≥30	44 (44.4)	34 (43.0)	24 (45.3)	
Gestasyonel week				
Mean±SD	30.9±8.2	31.6±8.3	35.2±6.7	**<0.001**
Gravida				
Mean±SD	2.3±1.2	2.3±1.2	2.4±1.4	0.972
1	27 (27.3)	21 (26.6)	15 (28.3)	
2	32 (32.3)	31 (39.2)	19 (35.8)	0.891
≥3	40 (40.4)	27 (34.2)	19 (35.8)	
Parite				
Mean±SD	1.0±0.8	1.0±1.1	1.0±0.9	0.747
0	29 (29.3)	29 (36.7)	19 (35.8)	
1	40 (40.4)	29 (36.7)	20 (37.7)	0.859
≥2	30 (30.3)	21 (26.6)	14 (26.4)	
Abortion				
Mean±SD	0.3±0.6	0.3±0.6	0.4±0.7	0.276
0	73 (73.7)	60 (75.9)	34 (64.2)	
≥1	26 (26.3)	19 (24.1)	19 (35.8)	0.304
Smoker				
No	97 (98.0)	78 (98.7)	45 (84.9)	**<0.001**
Yes	2 (2.0)	1 (1.3)	8 (15.1)	
Vaccine dose				
Patient with total vaccination		21(26.2)	29(54.7)	**<0.001**
1	–	12 (57.1)	9 (30.0)	0.126
2	–	9 (42.9)	20 (66.7)	

SD: Standard deviation; BMI: Body mass index.

given at 4–6 L/min per h by mask or nasal cannula in the service was found to be statistically significantly higher in groups 1 and 2 compared to group 3. There was no significant difference between the groups in terms of maternal mortality and morbidity. The number of patients discharged pregnant was found to be higher in groups 1 and 2, at 49% and 41%, respectively. 79.2% of the patients in group 3 were discharged after giving birth (p=0.003). There was no significant difference between the groups in terms of delivery type or caesarean section (C/S) indications. The number of C/S performed with an emergency maternal COVID-19 indication did not differ between the groups. It was found that COVID-19 did not increase the number of emergency or elective C/S indications.

Table 3 shows that when postpartum fetal characteristics were compared, no significant difference was found between the groups in terms of fetal birth weight, fetal COVID-19 detection rate, fetal sex ratios, neonatal morbidity, or mortality. The 1st min APGAR

Table 2: Comparison of obstetric outcomes and treatments between the groups

	1 (n=99)		2 (n=79)		3 (n=53)		p
	n	%	n	%	n	%	
Antibiotics							**<0.001**
No	54	54.5	50	63.3	48	90.6	
Ceftriaxone	41	41.4	29	36.7	5	9.4	
Azithromycin	4	4.0	–	–	–	–	
Steroids							**0.022**
No	78	80.4	57	73.1	49	92.5	
Yes	19	19.6	21	26.9	4	7.5	
Antenatal corticosteroids							**0.002**
No	86	87.8	66	83.5	50	94.3	
Betamethasone	11	11.2	3	3.8	1	1.9	
Dexamethasone	1	1.0	10	12.7	2	3.8	
Anticoagulants							**0.016**
No	8	8.1	1	1.3	–	–	
Yes	91	91.9	78	98.7	53	100	
O_2 requirement							**0.015**
No	72	72.7	55	69.6	48	90.6	
Yes	27	27.3	24	30.4	5	9.4	
Maternal ICU admission							0.656
No	91	91.9	71	89.9	50	94.3	
Yes	8	8.1	8	10.1	3	5.7	
Maternal morbidity							0.406
No	91	91.9	71	89.9	51	96.2	
Yes	8	8.1	8	10.1	2	3.8	
Maternal mortality							0.715
No	96	97.0	78	98.7	52	98.1	
Yes	3	3.0	1	1.3	1	1.9	
Pregnant discharged							**0.003**
No	50	50.5	46	58.2	42	79.2	
Yes	49	49.5	33	41.8	11	20.8	
Route of delivery							0.223
Cesarean section	39	81.3	32	74.4	26	65.0	
Vaginal delivery	9	18.8	11	25.6	14	35.0	
Cesarean indications							0.106
Elective no COVID	6	15.4	2	6.3	5	19.2	
Emergency fetal	7	17.9	7	21.9	2	7.7	
Emergency maternal COVID	12	30.8	8	25.0	2	7.7	
Emergency maternal no COVID	14	35.9	15	46.9	17	65.4)	

ICU: Intensive care unit; COVID: Coronavirus disease.

score was similar between the groups, but the 5th min APGAR score was 9.2, the highest in group 3 (p=0.005). When the rates of fetuses going to the neonatal ICU were examined, it was found that the highest rate was 17% in group 1 (p=0.007). When the length of hospital stay was compared, it was found to be the lowest in group 3, with 3.6±2.2 (p<0.001).

Table 3: Comparison of neonatal outcomes initial laboratory test results between the groups

	1	2	3	p
Birth weight (group), Mean±SD	2967±697	3067±682	3274±485	0.089
Apgar 1st min, Mean±SD	6.8±1.9	7.0±1.8	7.3±1.9	0.100
Apgar 5st min, Mean±SD	8.4±1.9	8.8±1.6	9.2±1.5	**0.005**
Fetal mortality				
No	46 (93.9)	42 (95.5)	39 (97.5)	0.715
Yes	3 (6.1)	2 (4.5)	1 (2.5)	
Neonatal COVID-19 positivity				
No	47 (100)	43 (100)	39 (97.5)	0.322
Yes	–	–	1 (2.5)	
NICU admission				
No	30 (63.8)	36 (83.7)	36 (90.0)	**0.007**
Yes	17 (36.2)	7 (16.3)	4 (10.0)	
Neonatal morbidity				
No	41 (85.4)	35 (79.5)	34 (85.0)	0.710
Yes	7 (14.6)	9 (20.5)	6 (15.0)	
Fetal sex				
Male	27 (57.4)	23 (53.5)	19 (47.5)	0.650
Female	20 (42.6)	20 (46.5)	21 (52.5)	
Length of hospital stay, Mean±SD	7.0±8.1	6.8±8.1	3.6±2.2	**<0.001**
WBC (10^3/uL), Mean±SD	18.8±29.7	34.0±52.0	20.0±30.6	**0.014**
Lymphocyte (10^3/mm^3), Mean±SD	1.1±1.1	2.4±3.2	1.2±1.9	0.061
AST (IU/L), Mean±SD	49.3±49.1	166.3±608.7	35.8±28.3	**0.011**
ALT (IU/L), Mean±SD	53.9±98.1	96.1±212.6	26.4±33.5	**<0.001**
LDH (IU/L), Mean±SD	329.0±205.5	420.4±531.9	290.5±103.2	**0.030**
Creatinine (mg/dL), Mean±SD	0.8±1.0	11.1±24.1	3.3±14.1	0.054
CRP (mg/dL), Mean±SD	35.1±56.6	82.9±71.2	60.2±50.5	**<0.001**
D dimer, Mean±SD	6.3±27.8	18.7±64.8	6.9±26.9	0.294
Ferritin (ng/mL), Mean±SD	75.0±171.2	259.7±1367.7	53.0±115.5	0.086
PT-INR, Mean±SD	3.2±14.9	10.8±29.0	2.9±12.9	**<0.001**

SD: Standard deviation; WBC: White blood cell; NICU: Neonatal intensive care unit; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; COVID-19: Coronavirus disease 19; CRP: C-reactive protein; LDH: lactatedehydrogenase; WBC: White blood cell; PT-INR: Prothrombin time-international normalized ratio.

Table 3 shows the laboratory parameters of the patients were compared between the groups, and the maximum white blood cell, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, and C-reactive protein numbers were found to be statistically significantly lower in group 3. Ferritin and D-dimer values were similar between the groups.

Compared with the logistic regression analysis between the groups, the number of patients who needed O_2 support was found to be lower in group 3 than in the other groups in Table 4. In addition, as age and body mass index (BMI) increased, O_2 requirement increased; the O_2 requirement decreased as gestational week and parity number increased. No significant correlation was found between smoking and the number of gravida and O_2 requirements.

The number of fetuses in need of neonatal ICU after birth was compared with logistic regression analysis among the groups, and it was found that the fetuses in group 3 needed the least neonatal ICU in Table 5. Maternal BMI was not found among the parameters affecting the neonatal ICU. There was no significant relationship between maternal smoking, fetal gender, and neonatal ICU. As the gestational week increased, the number of babies going to the neonatal ICU decreased.

Table 4: Comparison of needed O_2 support with the logistic regression analysis

Risk factor	OR (95% CI)	p
Group		
1	Reference	
2	1.35 (0.67–2.7)	0.394
3	0.29 (0.09–0.9)	**0.032**
Age	1.07 (1.00–1.14)	**0.028**
Gravida	1.36 (0.87–2.13)	0.173
Parity	0.50 (0.27–0.93)	**0.030**
Gestasyonel age at diagnosis	0.95 (0.92–0.99)	**0.030**
BMI (kg/m^2)	1.15 (1.04–1.2)	**0.004**
Smoker		
No	Reference	
Yes	2.19 (0.37–12.9)	0.383

OR: Odd ratios; CI: Confidence interval; BMI: Body mass index.

Table 5: Comparison of need neonatal intensive care unit after birth compared with logistic regression

Risk factor	OR (95% CI)	p
Group		
1	Reference	
2	0.46 (0.13–1.59)	0.220
3	0.21 (0.04–0.98)	**0.047**
Age	1.01 (0.91–1.11)	0.805
Gravida	1.28 (0.54–2.98)	0.568
Parity	0.90 (0.30–2.69)	0.864
Gestasyonel week	0.62 (0.50–0.78)	**<0.001**
BMI (kg/m^2)	1.08 (0.92–1.27)	0.309
Smoker		
No	Referans	
Yes	6.58 (0.80–54.0)	0.079
Fetal sex		
Female	Reference	
Male	0.90 (0.31–2.62)	0.854

OR: Odd ratios; CI: Confidence interval; BMI: Body mass index.

DISCUSSION

This study is a descriptive study of all pregnant patients with a confirmed COVID-19 infection treated at our tertiary care center hospital.

In this study, groups were separated according to the prevalence of possible variants. Severe COVID-19 in the groups decreased with neonatal ICU admission, obstetric complication rates, an increased prevalence of vaccines, and varying virus mutations. The significant increase in the experience of doctors caring for pregnant women with COVID-19 has also contributed to this development.

Various mutations have been observed in the SARS-CoV-2 genome over time. Although most of them are thought to have no significant impact on the course of COVID-19, some variants have raised serious concerns due to their rapid emergence.[13] A single-center, retrospective cohort study conducted at a tertiary center in the United States found that pregnant women diagnosed in the pre-delta variant period had higher rates of critical illness and adverse perinatal outcomes.[14] A multicenter prospective cohort study by Adhikari and SoRelle, including 1515 pregnant women, reported an increase in COVID-19-related morbidity after the Delta variant predominated in groups with low vaccine prevalence.[15] In another study by Sahin et al.,[16] it was found that the clinical course was more severe in pregnant women who were infected during the delta wave, and maternal mortality increased compared to the pre-delta period. Although the limited variant studies reviewed in the literature argue that the infection progresses more severely during the delta wave, our findings show that the patients in the range examined as probable delta variants have a better course compared to the pre-delta period. We think that the most important reason for this is related to the vaccination rate between the pre-delta and delta variants. All the relevant studies determined the subtype of viral variant via the date of infection instead of PCR analysis, but this subdivision is the weakest of all studies.

In unvaccinated pregnant women, who have infection during the delta variant wave was associated with increased oxygen support needs and higher maternal mortality compared to infection during the pre-delta wave; however, there is no clear evidence of a reduction in disease severity during the omicron wave (compared to the pre-delta period).[17] In the studies comparing the omicron variant and the delta variant, it is seen that the spread rate of the omicron variant is higher, but it causes less serious disease.[15] In our study, the group with the probable omicron variant and the group with probable delta variant were compared. In the group with the omicron variant, the O_2 requirement decreased, the number of days of hospitalization decreased, the need for additional antibiotic use decreased, the need for steroids for respiratory functions decreased, the APGAR increased at 5th min, and the admission to the neonatal ICU decreased. With all these findings, it was found that maternal and perinatal outcomes improved. In addition, the mean gestational week detected in the group with the probable Omicron variant was found to be higher. The reasons for the improvement of the severity of COVID-19 infection during the passing years are the gain of experience about the disease, which results in late and less hospitalization, which provides late preterm patient hospitalization and the rapid progression of vaccination policies for COVID-19. In addition, the lower rate of steroids for lung maturation and the higher rate of discharge from the hospital for pregnant patients in this group were also attributed to the same reason.

The majority of delta and omicron variants were found predominantly in COVID-19-positive pregnant women who were unvaccinated.[18] It was determined that vaccinated women who were infected during the omicron wave did not develop moderate and severe disease and were less likely to need oxygen support. The greatest contribution to this mechanism has been shown to be the increase in vaccination.[10] We also think that the better clinical course of the infection in patients in Group 3, where the omicron variant is frequently

observed, is related to the high rate of vaccination. We did not associate the reason why the need for maternal ICU was statistically close to each other in each group with the course of the disease. This may be due to the difference in the number of patients between the groups and the moderate-risk patients in group 3.

In the literature, C/S rates related to COVID-19 reported in systematic reviews and cohort studies range from 42.9% to 91–92%.[19] The type of delivery and C/S indications were similar between the groups. We think this is due to the fact that our clinical approach was based on obstetric indications and clinical urgency, as recommended by standard obstetric guidelines throughout the pandemic.[20]

Babies born to women who received a dose of the COVID-19 vaccine during the last 2 trimesters of pregnancy had a reduced risk of infection compared to babies born to unvaccinated women.[21] In our study, it was observed that the new-born ICU rate decreased and the APGAR 5th min score increased in the group where the vaccination rate increased.

Pregnancy is a mixed period accompanied by many physiological, endocrine, and immunological events.[22] The pregnant population becomes more vulnerable to some infectious agents due to the reasons listed.[23] Therefore, obstetricians should be more careful with a multidisciplinary approach in the treatment of infectious diseases.

The strengths of this study are that it provides holistic data on maternal and perinatal outcomes associated with COVID-19 infection during delta and omicron waves and compares these results over three time periods. To contribute to the literature on infectious respiratory diseases in the management of pregnant patients. The weaknesses of our study are that it is a retrospective study, virus genotyping cannot be performed, and it is grouped according to the estimated time interval.

There is no clear data on the rate of vaccination in pregnant women in our country,[24] but as seen in our study, the maternal and perinatal effects of COVID-19 decrease as the rate of vaccinated individuals increases.

CONCLUSION

In this study, which we aim to contribute to the literature on the management of infectious respiratory diseases in pregnancy, we think that patient management should be with a multidisciplinary and holistic perspective. We believe that preventive healthcare measures to prevent the disease and minimize its effects are more important in patient groups that are more difficult to manage, such as pregnancy.

Statement

Ethics Committee Approval: The İstanbul Medeniyet University Faculty of Medicine, Göztepe Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 30.03.2022, number: 0185).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – ED, AT; Design – ED; Supervision – ED; Resource – ED, HSB; Materials – CST, ODY; Data Collection and/or Processing – CST, ODY; Analysis and/or Interpretation – ED, HSB; Literature Search – ED, HSB; Writing – HSB; Critical Reviews – ED, AT.

Conflict of Interest: The authors have no conflict of interest to declare.

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