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AN INVESTIGATION INTO THE IMPACT OF CONTINUING OR TERMINATING PREGNANCY ON THE MATERNAL, FETAL AND DISEASE PROGRESSION OUTCOMES IN PREGNANT WOMEN WITH COVID-19

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Abstract

Introduction: *There is limited evidence regarding the potential impact of COVID-19 on pregnancy, fetuses, and its outcomes. Evaluating population-level data on these outcomes as soon as they become available will be crucial for identifying trends related to the COVID-19 pandemic and managing the disease in pregnant women and their offspring.*

Material and methods: *This study employed a descriptive-analytical approach based on the recorded hospital files. All pregnant mothers who presented to the hospitals and tested positive for COVID-19 were included. Data included background and initial information such as age, gender, maternal PCR positivity, COVID-19 vaccination, number of vaccinations, pregnancy count, number of deliveries after 20 weeks of gestation, miscarriage, gestational age at sonography, COVID-19 symptoms, pulmonary involvement, preterm labor, premature rupture of membranes, high blood pressure, preeclampsia, intrauterine fetal demise, deep vein thrombosis/pulmonary embolism, maternal death, pregnancy termination, age at pregnancy termination, reasons for pregnancy termination, method of pregnancy termination, hospitalization duration, maternal recovery, neonatal PCR positivity, Apgar score, neonatal weight, neonatal intensive care unit admission, and neonatal death. Blood factors at admission and discharge were also recorded.*

Results: *A total of 401 pregnant women were enrolled in the study, among whom 282 individuals underwent delivery due to labor pain, previous cesarean section, pain, and labor. Among the pregnant women with COVID-19, 385 (96%) tested positive for PCR. White blood cells, hemoglobin, platelet, alanine aminotransferase, serum ferritin levels, and D-dimer levels showed statistically significant differences before and after discharge. Maternal PCR positivity was significantly associated with first-trimester termination, and the number of COVID-19 vaccinations had a significant relationship with third-trimester termination. In cases of moderate to severe pulmonary involvement, white blood cells, hemoglobin, alanine aminotransferase, aspartate aminotransferase, serum ferritin levels, D-dimer levels, and thrombocytopenia showed a noticeable increase, statistically significant compared to mild cases.*

Conclusion: *This study suggests that the most common time for COVID-19 infection in pregnancy is the first and third trimesters, with clinical symptoms of fever and cough. Pregnancy termination during the inflammatory phase of COVID-19 in patients with severe involvement was associated with unfavorable outcomes for both the mother and fetus.*

Keywords: *pregnancy, outcome, fetal, coronavirus, COVID-19.*

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Introduction

In December 2019, a cluster of four cases of pneumonia with an unknown cause was reported to the World Health Organization in Wuhan, China [*Li Q et al., 2020*]. Since then, the coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has rapidly spread worldwide [*Permpalung N et al., 2023; Shou Y et al., 2023*]. On March 12, 2020, the World Health Organization declared the spread of this disease a pandemic. Many countries responded by restricting movement and diverting non-essential healthcare resources to focus on providing care for COVID-19 [*Walde J et al., 2023*].

Viral diseases during pregnancy pose a wide range of adverse outcomes for the fetus. For example, influenza infection has been associated with congenital abnormalities such as cleft palate, neural tube defects, and congenital heart defects [*Mosby L et al., 2011*]. Viruses can have long-term detrimental effects on the fetus. Moreover, elevated maternal inflammation levels in response to viral infection can impact various aspects of fetal brain development, leading to extensive neurological complications [*Liu H et al., 2020*]. For example, Zika virus infection transmitted to the fetus leads to a wide range of neurological abnormalities as well as an increased risk of fetal growth restriction and intrauterine death [*Chibueze E et al., 2017; Yang et al 2023*]. Since pregnant women are more susceptible to severe complications and illnesses resulting from infection with other coronaviruses, such as severe acute respiratory syndrome and Middle East respiratory syndrome, they have been recognized as a vulnerable group. They are recommended to take additional precautionary measures during the COVID-19 pandemic [*Azhar E et al., 2023; Kandeel M et al., 2023*]. To reduce transmission risks for pregnant women and healthcare workers, the International Federation of Gynecology and Obstetrics recommended suspending routine antenatal care and replacing it with virtual or telephonic consultations whenever possible [*Manchanda R et al., 2021; Popescu A et al., 2022*]. A COVID-19 infection can result in a mild illness where the virus is effectively cleared by the immune system or a severe disease with high mortality rates [*Cascella M et al., 2023*]. The position of pregnant women on this spectrum is not clearly understood. The immune system adapts during pregnancy to allow for the growth of a semi-allogeneic fetus [*PrabhuDas M et al., 2015*], and as a result, the immune response to infections during pregnancy is altered [*Eletreby R et al., 2023*]. Therefore, pregnant women with COVID-19 may have additional risk factors or synergistic effects on thrombosis. This hypothesis is supported by a case report describing the death of a woman at 29 weeks of pregnancy with COVID-19 due to a massive pulmonary embolism and aortic embolism [*Ahmed I et al., 2020*]. There is limited evidence regarding the potential impact of COVID-19 on pregnancy, the fetus, and its outcomes. Considering that seasonal influenza has been associated with higher rates of fetal loss [*Dorélien A, 2019*], and studies have examined the effects of other viral infections on fetal growth restriction, preterm birth, and pregnancy-related mortality [*Ferrazzi E et al., 2020; Whittaker E et al., 2020*], it is essential to monitor population-level data and conduct extensive testing to determine whether these findings also hold for COVID-19. As soon as they become available, the assessment of population-level data regarding these outcomes will be crucial for identifying trends related to the COVID-19 pandemic and managing the disease in pregnant women and their infants.

Material and methods

Study community, sampling, and research design

This is a descriptive-analytical study based on the registered files of Ahvaz Jundishapur University of Medical Sciences hospital. The study was conducted following approval from the Research Council and after obtaining the ethical code from the medical ethics committee of the University (IR.AJUMS.REC.1401.328). The research adhered to the principles outlined in the Declaration of Helsinki concerning human research. Admission of patients on the recommendation of another patient (referrals) to the clinic was carried out by the following departments: outpatient department – 85 (21.19%), public sector admission – 216 (53.86%) and neonatal intensive care unit admission 100 (24.93%). All pregnant mothers referred to hospitals were included. Moreover, the patient's request to withdraw from the study was excluded.

The information includes basic and basic data (age, sex, mother's positive PCR test, covid-19 vaccination, frequency of COVID-19 vaccination, number of pregnancies, number of deliveries after 20 weeks of pregnancy, abortion, gestational age by ultrasound, symptoms of COVID-19, pulmonary involvement, premature birth, premature rupture of fetal membranes, high blood pressure, pre-eclampsia, intrauterine fetal death, deep vein thrombosis/pulmonary embolism, maternal death, termination of pregnancy, age at termination of pregnancy, cause of termination of pregnancy, Pregnancy termination method, hospitalization time, maternal recovery, positive newborn PCR test, Apgar, newborn weight, The Neonatal Intensive Care Unit admission, and newborn death) as well as blood factors at visit and discharge time were recorded.

The method of calculating the sample size and selecting sampling method

In this study, to investigate the results of continuation or termination of pregnancy on the condition of the mother, fetus, and the course of the disease in pregnant women with COVID-19, for a confidence factor of 95% and a test power of 95%, the minimum number of people in the sample size of 268 people was considered. This number was calculated using G*power sample size software.

Statistical methods of analyzing the results

Quantitative variables were used to describe the center of the data from the mean (and/or median) and to describe the dispersion of the data from the standard deviation (and/or interquartile range). To describe the data in qualitative variables, frequency and percentage were used. The normality of the data was checked using Kolmogorov-Smirnov test and Q2-Q3 graph. All analyzes were performed using SPSS version 22 software. To compare multi-group variables, ANOVA test and k-square test were used for qualitative variables.

Results

A total of 401 pregnant women with an average age of 30.26 ± 6.26 (15-48) years were included in the study, of which 385 (96%) had a positive PCR test, and the highest rate of lung involvement was moderate (62.84%) and the lowest was severe (12.46%). During hospitalization, 282 people gave birth due to reasons (labor pain and previous cesarean history, labor pain, and exacerbation of the inflammatory phase of COVID-19, fetal distress, amniotic fluid stained with meconium, and preeclampsia syndrome). The highest number of births was related to the third trimester, where 61 cases had premature births and 221 had term births. The maternal mortality rate was reported as 3.24%, all of them had positive PCR test, 11 people had severe involvement and 2 had moderate involvement, among which 10 cases of termination of pregnancy were seen.

Also, the most common symptoms of COVID-19 were cough (87%), and the least were taste and smell disorders (11.47%). According to 1 and 2 tables, among the maternal outcomes, preterm delivery and then high blood pressure were the most common cases. In addition, 17 cases of abortion occurred. Among the newborns, 32 (7.98%) had a positive PCR test. The prevalence of infant mortality was reported to be 4.73%, among which only 3 infants tested positive (Table 1, Table 2).

Laboratory blood factors of pregnant mothers were collected at the time of admission and at the

TABLE 1

Descriptive information of referring pregnant mothers

Variables	Patients (Total = 401)
Age (year), Mean ± SD	6.26 ± 30.26
Positive PCR test, n (%)	385 (96)
COVID-19 vaccination, n (%)	109 (27.18)
Abortion, n (%)	17 (4.23)
Preterm births, n (%)	61 (15.21)
Premature ejaculation of the fetal membrane, n (%)	19 (4.73)
High blood pressure, n (%)	46 (11.47)
Pre-eclampsia, n (%)	20 (4.98)
Fetal intrauterine death, n (%)	12 (2.99)
Deep vein thrombosis/pulmonary embolism, n (%)	6 (1.49)
Mother's death, n (%)	13 (3.24)
Termination of pregnancy, n (%)	282 (36.15)
Pregnancy, n (%)	254 (63.3)
Improvement of mother, n (%)	343 (85.53)
Positive newborn PCR test, n (%)	32 (7.98)
Admitted to neonatal intensive care unit, n (%)	36 (8.9)
Infant death, n (%)	19 (4.73)

Table 2

Descriptive information of referring pregnant mothers

Variables		Patients (Total=401)
Covid-19 vaccination frequency, n (%)	1	34 (8.47)
	2	70 (17.45)
	3	5 (1.24)
Number of pregnancies (Gravid), n (%)	1	105 (26.18)
	2	98 (24.43)
	3	80 (19.95)
	4	27 (6.73)
	5	55 (13.71)
	6	24 (6.4)
	7	11 (5.9)
	8	1 (0.24)
Number of births (Para) after 20 weeks of gestation, n (%)	1	125 (31.17)
	2	81 (20.19)
	3	35 (8.72)
	4	17 (4.23)
	5	4 (0.99)
	6	1 (0.24)
Gestational age with ultrasound, n (%)	Date of last period	2 (0.49)
	First 3 months	330 (82.29)
	Second 3 Months	69 (17.2)
COVID-19 symptoms, n (%)	Cough	349 (87)
	Shortness of breath	198 (49.4)
	Fever	238 (87.03)
	Smell and taste disorders	46 (11.47)
	Headache	109 (27.18)
Pulmonary involvement, n (%)	Mild	99 (24.68)
	Medium	252 (62.84)
	Severe	50 (12.46)
Age of termination of pregnancy (weeks), n (%)	14 – 0	9 (2.24)
	28 – 14	11 (5.9)
	42 - 28	271 (67.58)
Cause of termination of pregnancy, n (%)	Acute COVID-19	10 (2.49)
	Labor pain	157 (39.15)
	Labor pain and history of cesarean section	80 (19.95)
	Fetal distress	15 (3.74)
	Amniotic fluid stained with meconium	10 (2.49)
	Preeclampsia Syndrome	10 (2.49)
Method of termination of pregnancy, n (%)	Natural Childbirth	157 (39.15)
	Cesarean section	125 (31.17)
Admission time, n (%)	1 week	243 (60.59)
	3 – 2 weeks	65 (16.20)
	More than 4 weeks	8 (1.99)
Apgar Score, n (%) for 1 minute	3 – 0	7 (1.74)
	6 – 4	15 (3.74)
	10 - 7	260 (64.83)
Apgar Score, n (%) for 5 minutes	3 – 0	4 (0.99)
	6 – 4	5 (1.24)
	10 - 7	273 (68.07)
Infant Weight, n (%)	3 – 0	9 (2.24)
	10 – 3	39 (9.72)
	50 – 10	95 (23.69)
	90 – 50	137 (34.16)

time of discharge from the hospital, which are shown in table 3. According to this table, white blood cells (p<0.001), hemoglobin (p<0.001), platelet (p<0.001), and alanine aminotransferase (p<0.001) were statistically significant before and after discharge.

Among the pregnancy outcomes, premature delivery and high blood pressure were statistically significant (p<0.05). The analytical results of the study were conducted based on the trimesters of pregnancy 0-14, 14-28, and 28-42 weeks and indicated that the mother's positive PCR test had a significant relationship with the first trimester (p=0.005), and more pregnant mothers in They had a positive test this trimester. Also, there was a significant relationship regarding the frequency of vaccination of COVID-19 with the third trimester (p=0.039) that mothers in this group received more vaccinations.

The analytical results of the study were performed based on the severity of lung involvement (mild, moderate, and severe) and indicated that the type of referral (p=0.036), positive maternal PCR test (p<0.001), abortion (p=0.037), and death Infants (p=0.023) had a significant relationship with severe involvement and more occurred in this group. There was also a significant relationship between the vaccination rate of mothers and mild lung involvement (p<0.001). In moderate to severe cases of pulmonary involvement in patients, a significant increase in liver enzymes, white blood cells, and lactate dehydrogenase was observed (p<0.05). In patients with mild involvement, an increase in liver enzymes was observed in the normal range, which was statistically significant (p<0.05), and these values were higher in patients at the time of referral than at the time of discharge.

DISCUSSION

The alarming global COVID-19 pandemic has posed challenges to the healthcare system regarding pregnant women's prevention, care, and treatment. This study investigated the individual characteristics, clinical symptoms, and laboratory findings of hospitalized pregnant women with COVID-19. In most studies, fever has been reported as the most common general clinical finding with respiratory involvement, including shortness of breath and cough. For example, studies in Italy [*Ferrazzi E et al., 2020*] reported fever in 70% of cases, cough in 80%, and shortness of breath in 70%. Similarly, Yan et al. (2020) found

TABLE 3

Test results of referring pregnant mothers

Variables	Average	Minimum	Maximum	Standard Deviation	P-Value
Primary white blood cells ($\times 10^9$/L)	11453.55	3800	30000	835.93	**< 0.001**
Clearance of white blood cells ($\times 10^9$/L)	8189.09	4500	18000	340.73	
Primary hemoglobin (*g/dL*)	10. 1	8.3	14.5	2.27	**< 0.001**
Clearance hemoglobin (*g/dL*)	10. 5	9.8	14.2	3. 81	
Primary platelet (per microliter)	225000.09	30000	481000	76. 54	**< 0.001**
Clearance platelet (per microliter)	219719.23	87000	668000	682.92	
Primary aspartate aminotransferase (*U/L*)	43. 47	16	480	5.29	0.737
Clearance aspartate aminotransferase (*U/L*)	51.78	21	420	4.30	
Primary alanine aminotransferase (*U/L*)	39.69	15	310	3.43	**< 0.001**
Clearance alanine aminotransferase (*U/L*)	35.22	24	270	5.62	
Primary bilirubin (*mg/dL*)	0.62	0.3	1.1	0.17	0.789
Clearance bilirubin (*mg/dL*)	0.5	0.4	1. 2	0.90	
Primary Blood urea nitrogen (*mg/dL*)	6.37	6	19	0.42	0.819
Clearance Blood urea nitrogen (*mg/dL*)	16.52	9	16	1.60	
Primary creatinine (*mg/dL*)	0.84	0.3	3.9	0.14	0.284
Clearance creatinine (*mg/dL*)	0.89	0.7	1.3	0.19	
Primary lactate dehydrogenase (*IU/L*)	225.4	220	1100	13.56	0.941
Clearance lactate dehydrogenase (*IU/L*)	288.74	215	470	48.37	

fever (9.50%) as the most common symptom, followed by sore throat (6.8%) and shortness of breath (6.2%). Liu et al. (2021) noted fever in 77% of cases and 23% reporting shortness of breath. In another study by Yang et al. (2020) in China, 60% of patients showed fever as the primary clinical finding. These consistent findings emphasize the significance of fever as a prevalent clinical symptom among pregnant women with COVID-19. Furthermore, other studies have reported fever as the most common clinical finding in pregnant women with COVID-19 [*Li Q et al., 2020; Liu D et al., 2020*]. Consistent with the present study findings, fever has been reported as the predominant clinical symptom in pregnant women with COVID-19 in other studies as well [*Sattari M et al., 2020; Sabetsarvestani P et al., 2021*]. Additionally, cough (87%) was observed in many patients, which aligns with the high prevalence of cough reported in the general population in other studies. Cough was reported as the most common clinical finding in pregnant women with COVID-19 [*Ellington S et al., 2020; Vouga M et al., 2021*]. Moreover, it has been observed that COVID-19 significantly increases adverse maternal and neonatal outcomes in pregnant women. In the present study, the rate of preterm birth in pregnant women with COVID-19 was 15.21%. Preterm birth is frequently mentioned as a common complication among individuals with COVID-19. In the study by Wölfel et al. (2020), who examined maternal and neonatal outcomes in two groups of COVID-19-positive mothers with severe symptoms and those with mild or asymptomatic symptoms, preterm birth was reported in 7.62% of individuals with severe symptoms and 6.36% in those without symptoms or with mild symptoms [*Vouga M et al., 2021*]. Additionally, in the study by Khoury et al. (2020), the rate of preterm birth was reported as 6.14%, and in the study by Zalud et al., it was reported as 15%, which is consistent with the findings of the present study [*Zlochiver V et al., 2021*]. Furthermore, in other studies, this rate has been reported between 4.5% and 61.2% [*Ferrazzi E et al., 2020; Khan S et al., 2020; Garcia-Ruiz I et al., 2021; Vergara-Merino L et al., 2021*].

In most studies, the rate of cesarean section in pregnant women with COVID-19 has been performed for various reasons, such as preserving fetal health and preventing further harm to the mother due to COVID-19 infection, being performed early and by cesarean section surgery. Regarding the mode of delivery in pregnant women with COVID-19, the results of the present study indicate a cesarean section rate of 31.17% in pregnant women with COVID-19. In one study, the cesarean section rate in affected individuals was 3.83%, and in the study by Sun et al. in the United States, the cesarean section rate was reported as 2.31% [*Son M et al., 2021; Vizheh M et al., 2021*]. In the multinational cohort study, the cesarean section rate in mothers with COVID-19 was 49% [*Villar J et al., 2021*]. In most studies, the cesarean section rate among affected individuals has increased. For example, this rate was 6.47% in Spanish pregnant women, 5.35% in American pregnant women with COVID-19, and 2.71% in Turkish pregnant women with COVID-19. In a review study by Juárez et al., this rate was reported as 78% [Juárez, Sol P et al., 2018; *Juan J et al., 2020; Marín Gabriel M et al., 2020; Oncel M et al., 2021; Vizheh M et al., 2021*]. However, other studies have reported this rate much lower, ranging from 16% to 24% [*Knight M et al., 2020; Verma S et al., 2020*]. During the early stages of the pandemic, the coronavirus caused complications and maternal mortality in pregnant women due to limited clinical experience in controlling and treating this disease during pregnancy. The present study reported 13 cases (3.24%) of maternal mortality. This rate has been reported between 0% and 11.1% in other studies, consistent with the present study's findings [*Lokken E et al., 2021*; *Papapanou M et al., 2021; Vergara-Merino L et al., 2021*]. In the present study, a prevalence of 11.47% for gestational hypertension and 4.98% for preeclampsia was observed in mothers with COVID-19. In the study by Vouga et al., a prevalence of 0.5% for gestational hypertension was reported. In the study by Baergen et al., the rate of gestational hypertension obtained was similar to the present study's findings [*Baergen R, Heller D, 2020; Vouga M et al., 2021*]. However, in other studies, the reported prevalence of gestational hypertension varied from 7% to 12.3% [*Lokken E et al., 2021; Zlochiver V et al., 2021*]. Regarding the prevalence of preeclampsia among affected individuals, Wei et al. (2021) reported a rate of 1.33%,

Moreover, this study identified a miscarriage rate of 4.23%, whereas in the specific study conducted by Wei et al. (2021), a rate of 3.7% was reported, indicating a higher occurrence compared to the rate observed in the present study, In the study by Knight et al., a rate of 1% for miscarriage was reported [*Knight M et al., 2020*]. On the other hand, neonatal hospitalization in neonatal intensive care unit is among the expected neonatal outcomes in women with COVID-19, with a rate of 8.9% observed in the present study. In a study in Spain, the rate of neonatal hospitalization in the neonatal intensive care unit was reported as 4.21%, which was close to the present study's findings [*Marín Gabriel M et al, 2020*]. However, Chen et al. (2020) reported a neonatal hospitalization rate of 6% in their study,

Due to the fluctuating regulation of the immune system during pregnancy, pregnant women are pro-inflammatory in the first and third trimesters, making them more susceptible to severe inflammation and a cytokine storm during COVID-19 infection [*Liu H et al., 2020; Tay M et al., 2020*]. This excessive inflammation can exacerbate the severity of COVID-19 disease and increase the mortality rate associated with this condition [*Jan F, 2020*].

The study results were also analyzed based on three-trimester subgroups (0-14, 14-28, and 28-42 weeks) and respiratory involvement (mild, moderate, and severe). This study found a significant association between a positive maternal PCR test and the first trimester. A significant association was also observed between the number of COVID-19 vaccinations and the third trimester.

Moreover, there was a significant association between abortion and the first trimester. Neonatal intensive care unit hospitalization was also significantly associated with the third trimester and neonatal mortality in the first trimester. Furthermore, the analytical results of the study based on the severity of respiratory involvement indicated significant associations between the mode of referral, maternal positive PCR test, abortion, neonatal mortality, and severe respiratory involvement. Additionally, there was a significant association between the number of COVID-19 vaccinations (Sinovac) and maternal improvement, as well as COVID-19 vaccination and mild respiratory involvement.

CONCLUSION

This study suggests that the most common COVID-19 infection during pregnancy, accompanied by clinical symptoms of fever and cough, occurs in the first and third trimesters. Termination of pregnancy during the inflammatory phase of COVID-19 in patients with severe involvement leads to unfavorable outcomes for both the mother and the fetus, while termination of pregnancy in the mild to moderate involvement group, according to obstetric indications, is associated with patient improvement and desirable outcomes. Therefore, severe respiratory involvement poses a significant risk factor for pregnant women. Consequently, identifying pregnant women with COVID-19 provides special assistance in maintaining the health of both the mother and the newborn, enabling healthcare managers and policymakers to develop appropriate health protocols for the care of pregnant women with COVID-19, utilizing the findings of this research and reported outcomes.

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