J Caring Sci, 2024, 13(2), 106-115
doi: 10.34172/jcs.33156
https://jcs.tbzmed.ac.ir

Original Article

Identifying the Risk Factors of Adverse Pregnancy Outcomes among Women with COVID-19: A Population-Based Case-Control Study in Southern Iran

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Article Info

Article History:
Received: September 8, 2023
Accepted: December 17, 2023
ePublished: April 13, 2024

Keywords:
COVID-19, Pregnancy, Maternal, Neonate

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Abstract

Introduction: Pregnant women and their fetuses are considered as high-risk groups during the COVID-19 pandemic. The aim of this study was to identify the risk factors of adverse pregnancy outcomes among women with COVID-19.

Methods: This case-control study was conducted among pregnant women who delivered live infants at least 60 days before data collection in Hormozgan Province, south of Iran, 2021. The case and control groups included women with and without the history of COVID-19, respectively. A 47-item checklist including demographic information of the mothers, maternal current and past medical history, maternal and fetal prenatal and post-natal outcomes; and other COVID-19 related outcomes was used. The logistic regression analysis was used for data analysis.

Results: A total of 1337 women (668 in case and 669 in control groups) participated in this study. The mean (SD) gestational age in the case and control groups were 32.83 (84.64) and 23.75 (6.93) weeks respectively. Maternal age and the incidence of abortion, obesity, and multiple pregnancies was higher in the COVID-19 group compared with the control group. The most common COVID-19 symptoms were myalgia (24.8%), cough (19.3%), fever (17.5%) and olfactory disorder (14.3%). The preventive factors against COVID-19 adverse pregnancy outcomes were low and normal body mass index, influenza vaccination history, and multivitamin consumption, while the risk factors were multiple pregnancies, abortion and preterm labor.

Conclusion: This study showed that pregnant women were to COVID-19. The identified risk factors for COVID-19 adverse pregnancy outcomes can be used to prioritized pregnant women in receiving COVID-19 related health services.

Introduction

Human coronavirus is among the most common pathogens causing respiratory infections and can result in death due to pneumonia and respiratory problems.[1] The COVID-19 outbreak was a great public health challenge.[2] The new coronavirus, called SARS-CoV-2, is the agent causing COVID-19 and can result in a life-threatening respiratory disease. COVID-19 has spread rapidly around the world and caused widespread public health problems.[3] Pregnant women and their fetuses are considered high-risk groups during the COVID-19 pandemic due to their susceptibility to upper respiratory tract infections due to their weak immune system. Furthermore, the reduced lung surface in pregnant women due to upper respiratory tract congestion caused by the high level of estrogen and progesterone also makes pregnant women prone to COVID-19 complications.[3-6] COVID-19 can affect all age groups and the incidence of COVID-19 in pregnancy has increased with the increase in the incidence of the disease in the population.[7] It should be noted that COVID-19 may change immune responses in both the mother and the fetus and affect the well-being of mothers and infants. It should be noted that the potential consequences of cytokine storm due to the infection may be exacerbated in pregnancy and result in more complications and mortality compared to non-pregnant women.[5]

Besides maternal concerns, infection in newborns may be asymptomatic or accompanied with mild symptoms. Although tachypnea, apnea, and cough are very important in identifying the infection in adults, but these symptoms may not be seen in infants. COVID-19 symptoms in newborns may include low grade fever, and body temperature instability, which frequently occurs in premature neonates. Infants might present with symptoms including malnutrition, lethargy, vomiting, diarrhea, and bloating.[8] In general, limited studies have been conducted on the effects of COVID-19 during and after pregnancy on mothers and newborns and the findings of these studies were contradictory.[9] For instance, a study by Banaei et al reported that COVID-19 was associated with adverse maternal outcomes, including fetal distress, preterm delivery, respiratory distress, thrombocytopenia with abnormal liver function, death, decreased fetal movement, intrauterine distress, anemia, hemorrhage, severe postpartum dyspnea, premature rupture of membranes, preterm delivery with meconium-stained amniotic fluid, and neonatal outcomes, including low birth weight, low Appearance, Pulse, Grimace, Activity, and Respiration)APGAR(score, and neonatal death.[10] In contrast, Zhang et al and Li et al and Fathi Najafi et al reported no to minimal maternal and neonatal outcomes in pregnant mothers with COVID-19.[11-13] The limitations of the previous studies may be listed as follows: (1) very small sample size, (2) lack of control group, and (3) lack of population-based studies. Therefore, there is a need for large population-based studies among pregnant women and newborns to identify the outcomes and risk factors for adverse pregnancy outcomes in COVID-19 patients. The findings of such studies will be helpful in designing strategies to maintain and promote maternal and neonatal health during COVID-19 pandemic.[14] The result of this study can also help health care professionals design health interventions to improve maternal and neonatal health during the COVID-19 pandemic. Therefore, the aim of this study was to investigate maternal and neonatal outcomes of COVID-19 in pregnancy in Southern Iran.

Materials and Methods

Study Design and Data Collection

This study was a retrospective case-control study that was conducted in Hormozgan province, south of Iran in 2021. Equal number of cases and controls were enrolled in this study (n = 910). Confirmation of the COVID-19 was based on the polymerase chain reaction (PCR) examination of nasopharyngeal swab along with chest computerized tomography (CT) scan. All pregnant mothers in Hormozgan province were included in the study from the beginning of the COVID-19 pandemic (4 November 2020) until October 2020.

Sampling Method and Study Population

The study population included all mothers with a history of COVID-19 (case group) and mothers without a history of COVID-19 (control group) who delivered to live infant at least 60 days from data collection. According to the Integrated Health System (SIB) database, 16139 pregnant mothers gave birth to live infants from 4 November 2020 to October 2020 in Iran, among which, 910 (5.5%) mothers with COVID-19 were from the Hormozgan province, Iran. As the number of the study population was equal to the sample size for the case group, data collection was performed using census sampling (All pregnant mothers with COVID-19 from the beginning of the epidemic to October 2020). Sampling in the control group was performed based on stratified random sampling method, where cities of the province were considered as classes.

As individual matching was not possible to match cases and controls in terms of maternal age and gestational age at delivery, group matching was performed in this study. Other than the main characteristics used for matching, it was attempted to homogenize groups based on the three important items in case-control studies, including selection, comparability, and exposure. In terms of "comparability", group matching as well as suitable statistical methods (comparison between the two groups and regression analysis) were used to reduce bias.

The main purpose of the study was explained to the participants orally. Subjects were asked to read and sign the informed consent form. Participants were assured that their information will be confidential. Participants were asked to complete the research questionnaires in a separate environment. After completing the questionnaires, the contact information of the researchers was provided to the participants if they wished to be notified of the findings of the study.

Outcome Measurements

A 47-item checklist including demographic information, influencing factors, maternal and fetal prenatal and post-natal outcomes; and other maternal and fetal outcomes due to COVID-19 was used to measure the study outcomes based on literature and library studies. The checklist validity was approved by an expert group (10 faculty members of obstetrics and gynecology). Sampling was conducted in the comprehensive urban and rural health centers in the cities of the Hormozgan province. The SIB integrated health system was used for data extraction. In order to standardize data collection procedure, necessary training was provided to enumerators regarding the proper way of completing the questionnaires.

Primary and Secondary Outcomes

Primary outcomes included factors related to COVID-19 in pregnancy, and maternal outcomes of COVID-19, while secondary outcomes included neonatal outcomes as follows:

1. COVID-19 related factors: location, age, literacy, occupation, income level, nationality, blood group and Rh, pregnancy and postpartum care; history of drug or tobacco use (cigarette smoking and hookah); body mass index, history of influenza vaccine injection, bacille Calmette-Guerin)BCG(vaccine

injection and skin color

2. Maternal obstetrics outcomes: abortion, preterm labor pain, rupture of membranes, stillbirth, COVID-19 related maternal complications, COVID-19 diagnosis method, gestational age, COVID-19 Symptoms, COVID-19 care, mental health and anxiety levels; maternal medications (in outpatient cases) and maternal death
3. Neonatal Outcomes: gender and weight, COVID-19 status, COVID-19 diagnosis method, neonatal age at the time of COVID-19 diagnosis, skin-to-skin contact between mother and infant, breastfeeding at birth, COVID-19 symptoms, neonatal health status and disease; neonatal nutrition status, and neonatal death.

Data Analysis

Data analysis was performed using the Statistical Package for Social Sciences (SPSS) version 24. Descriptive statistical methods, including mean (SD), were used to describe quantitative observations and frequency and percentage were used for qualitative observations. Normality of response variables was evaluated using the Shapiro-Wilk test. The independent t-test and the analysis of variance (ANOVA) were used to compare the means of normally distributed outcomes between groups, while the Mann-Whitney and Kruskal-Wallis tests were used to compare medians of the non-normally distributed outcomes between groups. The Chi-square and odds ratio (OR) were used for qualitative observations. Multiple logistic regression test was used to evaluate the relationship between dependent and independent variables controlling for confounders. Participants with missing data for a variable were excluded only in the analysis for the same variable. In all statistical testes $P<0.05$ was considered as statistical significance.

Results

A total of 1337 women were included in this study. The case groups (mothers with COVID-19) included 668 women and the control group included 669 women. The mean (SD) gestational age in the case and control groups were 32.83 (84.64) and 23.75 (6.93) weeks respectively. The most common COVID-19 diagnostic method was PCR (98%), while a combination of PCR and CT scan was used to confirm COVID-19 in 2% of women. The most common reported COVID-19 symptoms in case group were myalgia (24.8%), cough (19.3%), fever (17.5%) and olfactory disorder (14.3%). Only 13.3% of infected women were hospitalized due to COVID-19 during pregnancy and most of the admitted women (78.5%) did not require ICU admission. COVID-19 medications were administered to 54.6% of women. Generally, 88.6% of infected women recovered completely and only 2 (0.3%) maternal deaths due to COVID-19 were recorded.

The maternal and pregnancy characteristics of the participants depicts in Table 1. Both groups were not significantly different in terms of location, level of education of the mother or her spouse; mother or her souse's occupation; and income level ($P>0.05$). There was a significant difference in terms of age, gravida, number of abortions, and number of live children between case and control groups ($P<0.05$). All these variables were significantly higher among the case group compared to the control group. Gestational age at birth was significantly lower among the case group compared to the control group ($P=0.02$). Prevalence of influenza vaccination was significantly higher among the control group (54.1%) compared to the case group (54.1% vs 44.6%, respectively, $P=0.001$).

The rate of multiple pregnancy was significantly higher among the case group compared to the control group (4.2% vs 0.6%, respectively, $P<0.001$). Furthermore, the prevalence of overweight/obesity was significantly higher among case group compared to the control group (40% vs 30%, $P=0.003$). In the case group, 4.2% of the women did not take multivitamins, which was significantly higher compared to the control group (1.9%, $P=0.01$). Time of multivitamin initiation was not statistically different between the case and control groups ($P=0.83$).

Table 2 shows the comparison of pregnancy and childbirth outcomes between the case and control groups. There was a statistically significant difference between the case and control groups in terms of mode of delivery; so that the rate of cesarean section was significantly higher in the case group compared to the control group (40.7% vs 34.1%, respectively, $P=0.002$). According to the standard mental health screening tool, there was no statistically significant difference in the levels of anxiety, stress, and other mental disorders between case and control groups ($P>0.05$). The rate of abortion in the case group was significantly higher than the rate of abortion in the control group (1.8% vs 0.4%, $P=0.02$). The rate of preterm labor was significantly higher in the case group compared to the control group (11.7% vs 5.9%, respectively, $P<0.001$).

Ninety-six percent of the infants were apparently healthy at birth. Skin-to-skin contact was initiated immediately after birth and breastfeeding was initiated within four hours after birth in 89.2% of infants born to mother with COVID-19. There was a statistically significant difference in terms of skin-to-skin contact with mother and birth weight between the case and control groups ($P<0.001$). The rate of artificial feeding was significantly higher in case group compared to the control group (4.1% vs 1.7%, respectively, $P=0.006$). Furthermore, there was a significant difference in the distribution pattern of neonatal conditions between the case and control groups. While the incidence of intrauterine growth restriction (IUGR), congenital, and other neonates, was 4 (0.6%), 4 (0.6%), and 4 (0.6%), respectively, no such conditions were reported among the control group ($P<0.001$) (Table 3).

Multivariate logistic regression analysis was performed to identify the factor that were associated with COVID-19

Table 1. Comparison of maternal and obstetrics characteristics of the participants between the case and control groups

Maternal characteristics	Case (n=668)	Control (n=669)	*P* value*
Age (y), Mean (SD)	29.66)6.05(	28.60)5.81(	**0.001***
Gravida, Mean (SD)	2.68)1.52(	2.39)1.43(	**<0.001***
Parity, Mean (SD)	2.33)1.32(	2.15)1.21(	**0.012***
Number of abortions, Mean (SD)	0.34)0.65(	0.23)0.55(	**0.002***
Live children, Mean (SD)	2.34)1.31(	2.14)1.21(	**0.003***
Gestational age (wk), Mean (SD)	37.36)4.75(	37.93)4.16(	**0.021***
Blood group, No. (%)			
A	162 (24.3%)	156 (23.4%)	
B	185 (27.8%)	197 (29.5%)	0.46**
AB	42 (6.3%)	30 (4.5%)	
O	277 (41.6%)	284 (42.6%)	
Rh, No. (%)			
Positive	618 (92.5%)	626 (93.9%)	0.33**
Negative	50 (7.5%)	41 (6.1%)	
BMI (kg/m^2) , No. (%)			
<18.5	66 (9.9%)	92 (13.8%)	
18.5-24.9	332 (49.7%)	366 (54.8%)	**0.003****
25-29.9	187 (28%)	151 (22.6%)	
>30	83 (12.4%)	59 (8.8%)	
Mother's skin color, No. (%)			
black	13 (1.9%)	10 (1.5%)	
White	211 (31.5%)	187 (28%)	0.27**
brunette	444 (66.4%)	471 (70.5%)	
Smoking/addiction in 3rd trimester, No. (%)			
Yes	13 (1.9%)	16 (2.4%)	0.57**
No	655 (98.1%)	652 (97.6%)	
Drinking alcohol during pregnancy, No. (%)			
Yes	1 (0.1%)	2 (0.3%)	0.56**
No	667 (99.9%)	666 (99.7%)	
History of stillbirth, No. (%)			
Yes	6 (0.9%)	5 (0.7%)	0.76**
No	662 (99.1%)	663 (99.3%)	
History of preterm labor, No. (%)			
Yes	38 (5.7%)	30 (4.5%)	0.32**
No	630 (94.3%)	638 (95.5%)	
Multiple pregnancy, No. (%)			
Yes	28 (4.2%)	4 (0.6%)	**<0.001****
No	640 (95.8%)	664 (99.4%)	
Folic acid supplement, No. (%)			0.157**
Yes	668 (100%)	666 (99.7%)	
No	0 (0%)	2 (0.3%)	
Initiation of folic acid supplement, No. (%)			
Pre-pregnancy	122 (18.3%)	110 (16.5%)	
First trimester	543 (81.3%)	556 (83.5%)	0.152**
Second trimester	3 (0.4%)	0 (0%)	
Multivitamin supplement, No. (%)			
Yes	640 (95.8%)	655 (98.1%)	**0.018****
No	28 (4.2%)	13 (1.9%)	

Table 1. Continued.

Maternal characteristics	Case (n = 668)	Control (n = 669)	*P* value*
Initiation of multivitamin supplement, No. (%)			
First trimester	43 (6.7%)	42 (6.4%)	0.836**
Second trimester	603 (93.3%)	617 (93.6%)	
Influenza vaccination in the past year, No. (%)			
Yes	298 (44.6%)	361 (54.1%)	**0.001****
No	370 (55.4%)	306 (45.9%)	
BCG vaccination at birth, No. (%)			
Yes	648 (97.2%)	639 (95.7%)	0.143**
No	19 (2.8%)	29 (4.3%)	
Prenatal care, No. (%)			
Yes	587 (87.9%)	605 (90.6%)	0.112
No	81 (12.1%)	63 (9.4%)	

*Student t test; **Chi-square (χ^2)
n = number of participants; SD = standard deviation; t = Student t test; χ2 = chi-square test.
Bold values indicate statistically significant difference.

Table 2. Comparison of obstetrics complications between the case and control groups

Maternal characteristics	Case (n = 668)	Control (n = 669)	*P* value*
	Mean (SD)	Mean (SD)	
Mode of delivery			
CS	272 (40.7)	228 (34.1)	**0.002**
NVD	391 (58.4)	440 (65.9)	
Abortion			
Yes	12 (1.8)	3 (0.4)	**0.02**
No	656 (98.2)	665 (99.6)	
Genitourinary infection			
Yes	133 (19.9)	119 (17.8)	0.32
No	535 (80.1)	549 (82.2)	
Preterm labor			
Yes	78 (11.7)	39 (5.9)	**< 0.001**
No	590 (88.3)	626 (94.1)	
PROM			
Yes	4 (0.6)	4 (0.6)	0.99
No	652 (99.4)	654 (99.4)	
Prenatal anxiety, stress and mental disorders			
Yes	23 (3.5)	27 (4.1)	0.57
No	639 (96.5)	638 (95.9)	
Postnatal anxiety, stress and mental disorders			
Yes	8 (1.2)	17 (2.6)	0.07
No	655 (98.8)	647 (97.4)	

*Chi-square (χ^2)
n = number of participants; SD = standard deviation; χ^2 = chi-square test, PROM = premature rupture of membranes.
Bold values indicate statistically significant difference.

by including variables with significant difference between case and control groups in the model. In this model, the Hosmer and Lemeshow test was not significant (*P* = 0.35), which indicates that the test was appropriate for the data.

Table 3. Comparison of the clinical characteristics of newborns between the case and control groups

Newborns characteristics	Case (n = 668)	Control (n = 669)	*P* value*
	Mean (SD)	Mean (SD)	
Birth weight (g)	3028.84(540.27)	3107.98(443.36)	**0.001***
Gender			
Boy	353 (52.9)	346 (51.8)	0.680**
Girl	314 (47.1)	322 (48.2)	
KMC during first hours after birth			
Yes	596 (89.2)	633 (94.8)	**< 0.001****
No	72 (10.8)	35 (5.2)	
Feeding status			
Breast feeding	639 (95.9)	650 (98.3)	**0.006****
Artificial feeding	27 (4.1)	11 (1.7)	
Status of health & illness			
IUGR	4 (0.6)	0 (0)	**< 0.001****
Congenital anomalies	4 (0.6)	0 (0)	
Other diseases	4 (0.6)	0 (0)	
Seemingly healthy	655 (98.2)	669 (100)	

*Student t test; **Chi-square (χ^2)
n = number of participants; SD = standard deviation; t = Student t test; χ^2 = chi-square test, KMC = kangaroo mother care.
Bold values indicate statistically significant difference.

Based on the regression analysis, low body mass index (OR = 0.56, *P* = 0.02), normal body mass index (OR = 0.64, *P* = 0.03), history of influenza vaccination in the past year (OR = 1.45, *P* = 0.002), multiple pregnancies (OR = 0.13, *P* = 0.01), were significantly associated with COVID-19. It meant that women with low and normal body mass index were 0.44% and 0.36%, respectively less likely to develop COVID-19 compared to women with high body mass index. Women who had not been vaccinated against influenza in the past year were 0.45% more likely to develop COVID-19 compared to women who had been vaccinated against influenza. Women who did not have multiple pregnancies had a 0.86% lower chance of developing COVID-19 compared to those who had multiple pregnancies (Table 4).

Discussion

The results of the present study showed that pregnant women with COVID-19 were older and had higher incidence of abortions, obesity, and multiple pregnancies compared to the control group. However, there was no statistically significant difference between the history of smoking and alcohol between case and control groups. Some studies have reported that pregnant women with COVID-19 were more likely to be older, obese, have twin pregnancies, and have a history of high blood pressure compared to non-infected women. The study also indicated that alcohol use and smoking were less common among women with COVID-19, especially among primiparous women, compared to non-infected women.[15] It can be suggested that high-risk pregnancies, including twin pregnancies, make pregnant women more exposed to COVID-19 due to more frequent visits to medical centers that results in increased exposure to COVID-19.

Table 4. Regression analysis to determine the predictive role of maternal and obstetrics characteristics, obstetrics complications and newborn characteristics in differentiating women with COVID-19 from non-infected women

Variables	Logistic regression analysis		
	OR	*P*	95% CI
Age (y)	0.99	0.94	0.976, 1.023
Gravida	1.16	0.7	0.452, 2.980
Parity	0.65	0.39	0.245, 1.737
Number of abortions	1.00	0.99	0.386, 2.615
Live child	1.51	0.22	0.772, 2.954
Gestational age (wk)	1.00	0.74	0.975, 1.036
Birth weight (g)	1.00	0.22	1.000, 1.000
Mode of birth	1.23	0.09	0.963, 1.593
Abortion	2.52	0.36	0.348, 18.310
Multivitamin supplement	0.89	0.79	0.389, 2.066
Influenza vaccination	1.45	0.002	1.150, 1.829
Multiple pregnancy	0.13	0.01	0.030, 0.651
Feeding status	0.46	0.13	0.166, 1.278
KMC during first hours after birth	1.05	0.79	0.733, 1.505
Preterm labor	0.56	0.01	0.355, 0.897
BMI			
<18.5	0.56	0.02	0.342, 0.927
18.5-24.9	0.64	0.03	0.432, 0.964
25-29.9	0.84	0.42	0.550, 1.287
>30	RC	RC	RC
Neonatal health status/conditions			
IUGR	0.13	0.949	0.784, 20.320
Congenital anomalies	0.45	0.876	0.435, 2.487
Other diseases	0.23	0.443	0.132, 0.765
Seemingly healthy	RC	RC	RC

RC = Reference, KMC = Kangaroo mother care, BMI = Body mass index, r = Pearson Correlation Coefficient, OR = odds ratio.
Logistic regression analysis.
Bold values indicate statistically significant relationship.

The present study showed that higher body mass index of pregnant women was associated with increased risk of developing COVID-19. In a study conducted by Gao et al. a significant and positive relationship was reported between BMI and ICU admission due to COVID-19, and hospital admission or death due to COVID-19, which were in line with the findings of the present study.[16] Complications of obesity can be attributed to the presence of excess fat deposition in tissues, including liver, heart, or skeletal muscle, which results in metabolic dysfunction and insulin resistance. Type 2 diabetes, high blood pressure, cardiovascular disease and drug abuse can increase the risk of developing COVID-19 in obese women.[17]

The present study showed that pregnant women who were vaccinated against influenza had a lower risk of developing COVID-19 compared to unvaccinated women. A cohort study conducted by Candelli et al showed that influenza vaccination could be effective in reducing the risk for coronary heart disease and mortality, which was in line with the observed protective role of influenza vaccination against COVID-19 in the present study.[18] It is hypothesized that influenza vaccination may reduce the risk of other infectious diseases including COVID-19 due to pathophysiological mechanisms, including structural similarities in cell receptor ligands and antibody-reciprocal reaction and non-specific cell-response between influenza and COVID-19.[19,20]

The present study also showed that the use of multivitamins during pregnancy could reduce the incidence of COVID-19. Some vitamin deficiencies, including vitamin D, can increase the risk of developing COVID-19. Pregnant women can be more at risk for vitamin deficiency compared to non-pregnant women. The increased risk of vitamin D deficiency in pregnant women might be related to pregnancy, area of living, and limited sunlight exposure due to lockdown in COVID-19 pandemic. Proper intake of vitamin D supplements was previously reported to reduce the risk of viral respiratory infections.[21] Vitamin D may affect body response to COVID-19 is two ways. First, vitamin D increases the production of antimicrobial peptides in the respiratory epithelium, reduces the rate of virus replication, viral infection, and symptoms. Second, vitamin D reduces the inflammatory response to SARS CoV-2 by increasing the concentration of anti-inflammatory cytokines and decreasing the concentration of proinflammatory cytokines that increase lung damage.[22]

A systematic review conducted in 2021 showed that the COVID-19 can cause abortion and fetal loss through inflammation and placental insufficiency. In addition to placental inflammation, fibrin deposition and multiple villi infarcts in the placenta of mothers infected with SARS-CoV-2 can impair the transfer of nutrients from mother to fetus and lead to adverse pregnancy outcomes.[23] Due to the pandemic conditions, women had limited access to reproductive health services; therefore, unplanned pregnancies may have occurred during this period. On the other hand, women had limited access to reproductive health services during pregnancy and the risk of abortion and the negative pregnancy outcomes could increase. Some studies have shown that black or Hispanic pregnant women had a higher rate of COVID-19 and hospitalization compared to pregnant women of other races and ethnicities.[24,25] This may reinforce the hypothesis that race and ethnicity may influence the course of the disease in COVID-19. However, the present study found no statistically significant difference in skin color between affected and non-affected women. In general, differences between the findings of the present study and the previous studies may be due to differences in the course of the disease, symptoms and severity of the disease, or differences in the immune systems of mothers and fetuses. The immune system response in pregnancy is complex and varies based on gestational age, immune response, duration and severity of infection; and maternal and neonatal outcomes of COVID-19.

A systematic review and meta-analysis compared COVID-19 symptoms between pregnant and non-pregnant women. The study reported that the most common COVID-19 symptom in both pregnant and non-pregnant women were cough (pregnant: 48.5%; non-pregnant: 53.5%) followed by fever (pregnant: 75.5%; non-pregnant: 74%) and myalgia (26.5%).[26] This finding was in line with the findings of the present study, which reported that the most common symptoms in pregnant women with COVID-19 was fever, myalgia, and cough. In the study by Luo Q-Q et al. the most common symptoms were fever, cough and myalgia, respectively.[27]

Smith et al. showed that the incidence of preterm delivery, cesarean section, low birth weight, and neonatal intensive care unit (NICU) admission was higher among pregnant women with COVID-19 compared to the normal population, which was in line with the findings of the present study.[28] One of the mechanisms for increased incidence of preterm delivery in pregnant women with COVID-19 can be pre-placental hypoxia that can occur as a result of maternal respiratory disorders due to pneumonitis. This can promote a combination of anti-angiogenic and pro-inflammatory factors that cause endothelial dysfunction, end organ damage, and placenta insufficiency, and lead to partial fetal hypoxemia and finally, fetal hypoxia.[29] Viral infection during pregnancy can stimulate an abnormal response to opportunistic bacterial infections that may lead to preterm delivery.[30] Some studies reported that a large number of patients with COVID-19 experienced preterm labor, but the validity of these findings was questioned due to the lack of a control group.[31,32] The present study can confirm the results of the previous studies. The increase in the rate of fetal distress in newborn observed in mothers with COVID-19 in the present study reinforces the hypothesis that COVID-19 can act as a mediator and ultimately increase preterm delivery.[15]

Fetal distress has been reported as a consequence of COVID-19 in studies.[31-33] The cause of this finding is not known yet, but it might be due to preterm delivery or premature rupture of membranes (PROM). Therefore, fetal monitoring is recommended for early detection of these cases in the acute phase of the disease.

Increased incidence of cesarean delivery in pregnant women with COVID-19 has been previously reported[15,34] and was similar to the findings of the present study. Cesarean delivery is not directly related to COVID-19 severity in mother or fetus. Only a few studies reported that Caesarean section was performed due to maternal complications and fetal distress related to COVID-19. As a result, other clinical and non-clinical factors, including preeclampsia, preterm delivery, management of maternal respiratory disease, and the need to expedite delivery to stabilize mother's condition, improve maternal ventilation and prevent vertical transmission, should be considered in choosing the method of delivery. However, no contraindications for Caesarean section in pregnant women with COVID-19 have been reported yet.[15] Th increased rate of Caesarean section and preterm labor may potentially be due to iatrogenic reasons.[33]

Similar to the findings of the present study, an increase in the incidence of low birth weight has been reported in other studies.[28] Preterm delivery may be associated with increased prevalence of low birth weight and higher rates of NICU admission. It is important to note that COVID-19, as an acute infection, may have minor effects on birth weight. However, serial ultrasound assessments to evaluate the risk of IUGR is recommended in early pregnancy infections, and in pregnant women with chronic hypoxia.[34] Furthermore, a systematic review showed that the most common obstetric findings in pregnant women with COVID-19 were preterm delivery, preeclampsia, hypertension, fetal distress, and fetal growth restriction.[35]

The present study showed a statistically significant difference in the health status of the infant between pregnant women with COVID-19 and non-infected women. In another study, the incidence of IUGR, LBW and NICU admission was higher in neonates born to an infected mother compared to the non-infected group.[36] Low expression of angiotensin converting enzyme-2 (ACE-2) during pregnancy was found to be associated with preeclampsia and IUGR in humans and various animal models.[37-40] Thus, decrease in ACE2 due to COVID-19 may be a risk factor for placental vascular dysfunction, maternal hypertension, and adverse pregnancy-related consequences of placenta dysfunction, as well as exacerbation of pre-existing conditions in pregnancy.

These complications may lead to increased incidence of IUGR or exacerbation of pre-existing IUGR.[37] One study also showed that the rate of severe neonatal complications, including NICU length of stay of 7 days or more, as well as severe neonatal complications and their components, were significantly higher in women with COVID-19 compared to non-infected pregnant women. Increased neonatal risk persisted after adjusting for the effect of history for preterm delivery and preterm delivery in the current pregnancy. Therefore, it is possible that COVID-19 may have direct effects on adverse neonatal outcomes.[41]

The present study showed that the number of live children was significantly higher in pregnant women with COVID-19 compared to non-infected pregnant women. The risk of maternal and neonatal mortality due to COVID-19 has been reported to be very low in some studies.[32,33,41-46] Although COVID-19 is a disease that has resulted in a large death toll, it is not yet possible to determine whether these deaths are related to COVID-19 infection.[44,47]

In the present study, the rate of breastfeeding was lower in infants of infected mothers compared to non-infected mothers. Some studies reported that the rate of breastfeeding was as low as 28.6% among women with COVID-19. Neonatal morbidity, low birth weight and preterm neonates, as well as inability of infected mother to breastfeed due to COVID-19 symptoms or pregnancy and childbirth complications are more common in these women. These factors may reduce the rate of breastfeeding and thus increase the need for formula feeding. One of the limitations of this study was the difficulty in matching the case and control groups.

Conclusion

The results of the present study showed that pregnant women are one among the vulnerable groups for COVID-19, based on the related risk factors, high-risk pregnant women should be prioritized to receive COVID-19 related health services. Women with COVID-19 were older and had higher incidence of abortions, obesity, and multiple pregnancies compared to the control group. However, based on the regression analysis, the effect of age, parity, and number of abortions was not significant. Lifestyle modification, evaluation and treatment of vitamin deficiency in preconception care and increasing the number of pregnancy care-related to abortions and preterm labor among pregnant women during COVID-19 pandemic is recommended.

Acknowledgements

We hereby highly appreciate the cooperation of the personnel of the Mother and Child Welfare Research Center and the Hormozgan University of Medical Sciences. The authors would like to thank Ms. Delaram Kamali, Masoumeh Kheirmand Parizi, Elham Salehi and Ms. Roghaieh Mandegari for their help in conducting this research.

Research Highlights

What is the current knowledge?

- The coronavirus disease 2019 (COVID-19) has emerged global threat to the health of the world population. Pregnant women are among the high risk population.
- COVID-19 is reported to be associated with negative pregnancy outcomes.

What is new here?

- COVID-19 was associated with higher risk for abortion and preterm labor.
- Normal to low body weight, history of influenza vaccination and multivitamin consumption had a preventive role against COVID-19.
- Lifestyle modification, evaluation, and treatment of vitamin deficiency in preconception care are of greater importance in COVID-19 pandemic. Furthermore, pregnant mother should be visited more frequently during the pandemic.

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Competing Interests

The authors declare that they have no competing interests.

Data Availability Statement

The datasets generated and/or analyzed during the current study are not publicly available due to university rules and regulation of data ownership but are available from the corresponding author on reasonable request.

Ethical Approval

This study was approved by the Ethical Committee of Hormozgan University of Medical Sciences. Signed informed consent was obtained from the study participants prior to the study. All methods were carried out in accordance with relevant guidelines and regulations in ethical approval and consent to participate section.

Funding
This study received fund from Hormozgan University of Medical Sciences.

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