Original Article

ISSN: 1735-0344 *Tanaffos 2024; 23(1): 73-82*

TANAFFOS

Relationships between Fetal and Neonatal Outcomes and Spectrum of COVID-19 Disease in Pregnant Women

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Received: 11 December 2022
Accepted: 22 November 2023

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Background: Due to the high prevalence of COVID-19 and the prevention and control of adverse fetal and neonatal outcomes in pregnant women, including vertical transmission, this study was performed to describe the fetal and neonatal outcomes of pregnancy with a spectrum of COVID-19 disease during pregnancy in Iran.

Materials and Methods: In this cross-sectional study, we analyzed the medical records of 258 pregnant women admitted to the Forghani Hospital, Qom, Iran, from 18 February 2020, to May 10, 2021. PCR-RT or respiratory compromise in the presence of marked radiographic changes of COVID-19 in the lungs, or both COVID-19 disease confirmed COVID-19 disease. Then, we collected the disease spectrum of COVID-19 and fetal and neonatal outcomes from patient records.

Results: The findings of our study showed that out of 258 pregnant women who were hospitalized due to COVID-19, 79.8% had mild to moderate disease, 16.7% had severe COVID-19, and 3.5% were in the critical stage. After adjusting for the confounding variables, the severity of the disease was significantly associated with adverse fetal and neonatal outcomes such as fetal distress, Intra Uterine Growth Restriction (IUGR), preterm delivery, and Low Birth Weight (LBW), and low first minute Apgar score. However, the severity of COVID-19 was not a predictor of spontaneous preterm delivery, admission to NICU, low Apgar scores at 5 minutes, vertical transmission, stillbirth, and neonatal death.

Conclusion: Neonates of mothers with the severe and critical stage of COVID-19 are exposed to higher potential risks such as fetal distress, IUGR, preterm delivery, LBW, and low Apgar scores at 1 minute than women with mild to moderate disease.

Keywords: Fetal; Neonatal; Outcomes; Pregnancy; Severity of COVID-19

INTRODUCTION

On January 30, 2020, the World Health Organization (WHO) declared the outbreak of COVID-19 respiratory disease caused by the 2019 novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), as the sixth public health emergency and international concern (1). Common symptoms included fever (80-100%), cough (59-82%), fatigue and muscle aches (70-44%), and shortness of breath, and less common symptoms included headache, sputum, and diarrhea. Pneumonia, and infiltration or pulmonary consolidation are seen in 50% of patients (2). An increase in blood neutrophils count and a decreased number of circulating lymphocytes are directly related to the severity of the disease and the mortality rate (3). The mortality rate from COVID-19 is predicted to be 3-4% (4). Coronavirus is associated with a wide spectrum of

clinical manifestations, from asymptomatic or mild disease to severe pneumonia and death (5, 6). A systematic review study reported that the severity of pathogenicity in pregnant women was 95.6% mild, 3.6% severe, and 0.8% critical (7). The severity of the disease varies in different studies, and several factors such as maternal age, obesity, and underlying disease (diabetes and hypertension) affect the severity of the disease and mortality (6, 8, 9). Increasing oxygen consumption and decreasing functional residual capacity, which occurs in normal pregnancies, may facilitate maternal deterioration in pregnant women with pneumonia (10). Also, " excessive uterine distension from multiple gestations or severe polyhydramnios in the third trimester may further compromise pulmonary function" (11). Experience with other viral infections has shown that pregnant women are more susceptible to severe coronavirus infection due to physiological and immunological changes in pregnancy (12-14). Hence, the effects of COVID-19 on pregnancy are worrying (15). But, an increase in pathogenicity has been evident during previous viral epidemics (16). In the influenza epidemic, 10% of all deaths occur in pregnant women. The mortality rate in pregnant women is twice as high as in infected women who are not pregnant (17). The most common adverse maternal and fetal outcomes associated with maternal viral pneumonia as Severe Acute Respiratory Syndrome (SARS-CoV), Middle East Respiratory Syndrome (MERS-CoV), and influenza including preterm membrane rupture (PROM), preterm delivery (PTL), intrauterine fetal death (IUFD), intrauterine growth restriction (IUGR), and neonatal death (16, 18, 19). Vertical transmission of other viral infections from mother to fetus has not yet been established (16, 19), and there is no evidence of vertical transmission of COVID-19, especially in the third trimester of pregnancy (20).

Due to the high prevalence of COVID-19 and the prevention and control of adverse fetal and neonatal outcomes in pregnant women, including vertical transmission, this study was performed to describe the fetal and neonatal outcomes of pregnancies with the spectrum of COVID-19 disease during pregnancy in Iran..

MATERIALS AND METHODS

A cross-sectional study was performed on 258 pregnant women admitted to the Forghani Hospital, Qom, Iran. Sampling in this study was started from the time of registration of the first case of coronavirus disease (COVID-19) in Iran (18 February 2020), and considering that the spread of this disease has experienced various ups and downs in Iran, the sample recruitment continued until the fourth wave of May 10, 2021. All methods were carried out by relevant guidelines and regulations under ethics approval (Medical Ethical Committee of the Qom University of Medical Science (IR.MUQ.REC.1399.152). We also received written informed consent from the participants. Our study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for cross-sectional studies (21).

Recruitment and data collection

In our study, inclusion criteria included all pregnant women whose COVID-19 disease was confirmed by detection in viral RNA on polymerase chain reaction testing of nasopharyngeal swab or respiratory compromise in the presence of marked radiographic changes of COVID-19 in the lungs, or both. Then the midwifery and reproductive health specialist collected the demographic and obstetric characteristics of pregnant women from patient records.

We collected demographic and obstetric characteristics such as maternal age, body mass index, ethnicity, parity, twins, gestational age, and underlying diseases.

The severity of COVID-19 in pregnancy was classified according to the Maternal and Fetal Medical Association (sMFM) as follows: Mild illness: Mild symptoms such as fever, fatigue, cough, and/or less common features of COVID-19. Severe illness: tachypnea (respiration rate> 30 breaths per minute), hypoxia (93% oxygen saturation in

room air or PaO_2 / FiO_2 <300 mm Hg), or> 50% lung involvement on imaging. The critical stage of the disease was characterized by respiratory failure, shock, or dysfunction of several organs. To define severe illness in this study, shortness of breath is defined as shortness of breath reported by the patient at rest. The critical stage of COVID-19 is defined as respiratory failure required for mechanical ventilation, septic shock, dysfunction, or multiple organ failure (22, 23). Also, we collected fetal outcomes, including abortion rates, fetal distress, intrauterine growth restriction, and stillbirth. Neonatal outcomes include spontaneous preterm delivery <37 weeks' gestation, preterm delivery <37 weeks' gestation, low birth weight < 2500 g, abnormal Apgar score of the first and fifth minutes <7, vertical transmission rate, hospitalization in NICU, stillbirths (est24 weeks' gestation) and infant mortality from the hospital report of pregnant women. If some of the required information is not included in the patients' files, the required information is obtained through a telephone interview.

Since previous similar studies determined the prevalence of preterm delivery at <37 wk.as 88% in the critical group and 27 % in the -severe group (24), as well as α=0.05, β=0.20, and fα=7.8 in the Gigi table, we calculated a sample size of 217 patients, which was increased to 258 patients taking into account the rate of loss. Probability values less than 0.05 were considered significant.

Statistical analysis

We used the absolute and relative frequency distributions for statistical analysis in descriptive statistics, the chi-square univariate statistical test to show the dependence between categorical variables, and Regression logistic analysis to investigate the relationship between COVID-19 diseases and predict fetal and neonatal outcomes and to control the interfering factors in fetal and neonatal outcomes we simultaneously entered variables of maternal age, body mass index, ethnicity, parity, pregnancy trimester, and having underlying diseases into regression analysis. We used SPSS version 22 statistical software to perform statistical calculations in the present study considering a significance level of less than 0.05.

RESULTS

Relationships between demographics and obstetrics characteristics of pregnant women and disease spectrum of COVID-19 infection

Demographic and obstetric characteristics were reported in Table 1. The findings of our study showed that out of 258 pregnant women who were hospitalized due to symptoms of the novel coronavirus disease 2019 (COVID-19) and positive PCR test or CT scan, 206 (79.8%) had mild to moderate disease, 43 (16.7%) had severe COVID 19 and 9 (3.5%) were in critical stage. Overall, the mean age was 29 years; pregnant women with severe and critical coronavirus disease were significantly older than women with mild and moderate disease (p=0.03). Also, pregnant women with severe and critical coronavirus disease had a higher body mass index (BMI) than women with mild and moderate disease (p=0.04). Among 258 Pregnant women, 45 (17.4%) were Afghan, and the findings of our study showed that the severity of the disease has a significant relationship with ethnicity (p<0.001). In our study, 31 of 43 (72.1%) women with severe disease and 7 of 9 (77.8 %) women with critical coronavirus disease were in the third trimester of pregnancy.

In the critical stage of the disease, 88.9% of women were multiparous, and a significant relationship was observed between parity and severity of coronavirus disease (p=0.02). In women with the critical coronavirus disease, 6 of 9 (66.7%) had underlying conditions (diabetes, hypertension). The findings of our study showed that the severity of the disease has a significant relationship with the history of the underlying disease (p>0.001).

Drugs used to treat COVID-19, including hydroxychloroquine (13.2%), azithromycin (36.8%), ceftriaxone (48.4%), or other research drugs (e.g., Remdesivir (16.7%) and plasma injections (2.3%)) were recorded from the patient's medical records. Also, the findings of our study showed that the severity of the

disease has a significant relationship with a history of taking the drugs mentioned above (p>0.001). The type of consumption drugs has been published in detail in another article by the authors in the field of disease severity and maternal outcome (25).

Relationships between disease spectrum of COVID-19 infection and fetal and neonatal outcome

Fisher's exact test was used to evaluate the relationship between the severity of COVID-19 and fetal and neonatal outcomes (Table 2). The findings of our study showed that fetal distress, Intra Uterine Growth Restriction (IUGR), stillbirth, spontaneous preterm birth, and preterm birth, LBW, required admission to NICU, Vertical transmission, and APGAR scores at 1&5 minute <7 are significantly associated with the severity of disease (p<0.05).

The mean birth weight was 2962.6± 580.08 in the mild to moderate disease group, 2490.2±542.6 in the severe disease group, and 1881.1±717.7 in the critical disease group.

Also, we used logistic regression analysis for the two-position variable to investigate the relationship between the severity of COVID-19 and fetal and neonatal outcomes. The variables of maternal age, maternal BMI and ethnicity, pregnancy trimester, parity, and underlying diseases were considered confounding variables in fetal and neonatal outcomes that simultaneously entered into regression analysis with the severity of COVID-19. After adjusting the confounding variables, the results of our study showed that the severity of the disease was significantly associated with adverse fetal and neonatal outcomes such as fetal distress, IUGR, preterm delivery, LBW, and first-minute Apgar score of less than seven.

The severity of COVID-19 increases the odds of fetal distress threefold (OR = 3.09, 95% CI = 4.1-117.6). Also, the severity of COVID-19 increases the rate of IUGR by 5.4 times with CI = 5.3-92.6. Also, findings show that with the increasing severity of the disease, preterm delivery increases (OR = 2.09, 95% CI = 2.1-30.5). The odds of LBW was 3.8 times, and with increasing severity of the disease, the birth weight decreased (OR = 3.8, 95% CI = 3.4-579.3). Finally, the severity of COVID-19 had a significant effect on the Apgar score at 1 minute, with the score decreasing as the disease severity increased (OR = 2.3, 95% CI = 1.2-90.5) (Table 3).

Table 1. Relationships between, demographic and obstetric characteristics of pregnant women and the severity of COVID-19

Characteristic	Overall (N = 258) (%)	Mild and moderate (N = 206) (%)	Severe COVID-19 (N = 43) (%)	Critical (N = 9) (%)	P value
Maternal age (y)					
< 25	58(22.5)	54(26.2)	3(7.0)	1(11.1)	0.03
25-35	145(56.2)	113(54.9)	26(60.5)	6(66.7)	
> 35	55(21.3)	39(18.9)	14(32.6)	2(22.2)	
BMI					
Yes	49(19.0)	33(16.0)	13(30.2)	3(33.3)	0.04
No	209(81.0)	173(84.0)	30(69.8)	6(66.7)	
Ethnicity					
Iranian	213(82.6)	179(86.9)	29(67.4)	5(55.6)	0.002
Afghan	45(17.4)	27(13.1)	14(32.6)	4(44.4)	
Trimester of pregnancy					
First trimester	30(11.6)	28(13.5)	2(4.7)	0(0.0)	0.02
Second trimester	70(27.1)	58(28.2)	10(23.3)	2(22.2)	
Third trimester	158(61.3)	120(58.3)	31(72.1)	7(77.8)	
Parity					
Nulliparous	62(24.0)	57(27.7)	4(9.3)	1(11.1)	0.02
Multiparous	196(76.0)	149(72.3)	39(90.7)	8(88.9)	
Pregnancy					
Twins	6(2.3)	3(1.5)	3(7.0)	0(0.0)	0.08
Single	252(97.7)	203(98.5)	40(93.0)	9(100.0)	
Underlying conditions (Diabetes, Hypertension)					
No	181(70.2)	156(75.7)	22(51.2)	3(33.3)	0.000
Yes	77(29.8)	50(24.3)	21(48.8)	6(66.7)	

Table 2. Relationships between severity of COVID-19 and fetal and neonatal outcomes

Fetal Outcomes	Overall (N = 258) (%)	Mild and moderate (N = 206) (%)	Severe COVID-19 (N = 43) (%)	Critical (N = 9) (%)	P value
Abortion					
No	257(99.6)	205(99.5)	43(100.0)	9(100.0)	0.88
Yes	1(0.4)	1(0.5)	0(0.0)	0(0.0)	
Fetal Distress					
No	227(88.0)	191(92.7)	33(76.7)	3(33.3)	**0.000**
Yes	31(12.)	15(7.3)	10(23.3)	6(66.7)	
IUGR					
No	254(98.4)	205(99.5)	43(100.0)	6(66.7)	**0.000**
Yes	4(1.6)	1(0.5)	0(0.0)	3(33.3)	
Intrauterine fetal death (IUFD)					
No	256(99.2)	206(100.0)	43(100.0)	7(77.8)	**0.001**
Yes	2(0.8)	0(0.0)	0(0.0)	2(22.2)	
Neonatal Outcomes	**(N = 96)**	**(N = 67) (%)**	**(N = 20) (%)**	**(N = 9) (%)**	
Spontaneous preterm birth					
No	80(83.7)	59(88.1)	17(85.0)	4(44.4)	0.007
Yes	16(16.3)	8(11.9)	3(15.0)	5(55.6)	
Neonatal Outcomes	**(N = 95)**	**(N = 67) (%)**	**(N = 20) (%)**	**(N = 8) (%)**	
Preterm birth					
No	54(56.8)	49(73.1)	5(25.0)	0(0.0)	0.000
Yes	41(43.2)	18(26.9)	15(75.0)	8(100.0)	
Low Birth Weight (LBW)					
No	69(72.6)	59(88.1)	9(45.0)	1(12.5)	0.000
Yes	26(27.4)	8(11.9)	11(55.0)	7(87.5)	
Admission to NICU					
No	68(71.6)	53(79.1)	11(55.0)	4(50.0)	0.01
Yes	27(28.4)	14(20.9)	9(45.0)	4(50.0)	
Vertical transmission					
No	91(95.8)	67(100.0)	19(95.0)	5(62.5)	0.000
Yes	4(4.2)	0(0.0)	1(5.0)	3(37.5)	
Neonatal SEPSIS					
No	95(100.0)	67(100.0)	20(100.0)	8(100.0)	1.0
Apgar scores at 1-min <7					
No	85(89.5)	63(94.0)	18(90.0)	4(50.0)	0.003
Yes	10(10.5)	4(6.0)	2(10.0)	4(50.0)	
Apgar scores at 5-min <7					
No	91(95.8)	66(98.5)	19(95.0)	6(75.0)	0.01
Yes	4(4.2)	1(1.5)	1(5.0)	2(25.0)	
Neonatal death					
No	95(100.0)	67(100.0)	20(100.0)	8(100.0)	1.0

Table 3. Logistic regression model testing the association between severity of COVID-19 and Fetal and Neonatal Outcomes

	Crud OR	P	Adj. OR	P	(95% CI ORb)
Fetal distress	3.2	0.000	3.09	0.000	4.1-117.6
IUGR	5.1	0.000	5.4	0.004	5.3-92.6
Intrauterine fetal death (IUFD)	19.9	0.9	35.2	0.9	-
Spontaneous preterm birth	2.22	0.01	1.7	0.08	0.7-42.6
Preterm birth	2.1	0.002	2.09	0.002	2.1- 30.5
Low birth weight (LBW)	3.9	0.001	3.8	0.004	3.4-579.3
Admission to NICU	1.1	0.03	1.03	0.2	0.5-15.8
Vertical transmission	20.6	0.9	46.6	0.9	-
Abnormal APGAR 1	2.7	0.002	2.3	0.03	1.2-90.5
Abnormal APGAR5	3.09	0.01	0.4	0.1	-

Abbreviations: CI: confidence interval; OR: odds ratio

b Adjusted for maternal age, BMI, ethnicity, trimester, parity, and preexisting problem.

DISCUSSION

In this retrospective study, we evaluated the relationship between the disease spectrum of COVID-19 infection during pregnancy and fetal and neonatal outcomes. In general, our study showed that infection with COVID-19 caused mild and moderate diseases in 79.8%, severe diseases in 16.6%, and critical diseases in 3.5% of pregnant women. The factors associated with the severity of COVID-19 were increased maternal age, BMI, Afghan ethnicity, gestational age and parity, and underlying diseases. Then, the findings of our study show that the severity of COVID-19, after adjusting for confounding variables such as maternal age, BMI, ethnicity, trimester of pregnancy, parity, and underlying diseases, is significantly associated with fetal and neonatal outcomes as fetal distress, IUGR, preterm delivery, LBW and Apgar scores at 1 minute<7. However, the severity of COVID-19 was not a predictor of spontaneous preterm delivery, admission to NICU, Apgar scores at 5minute<7, vertical transmission, stillbirth, and neonatal death.

Relationships between demographics and obstetrics characteristics of pregnant women and spectrum of COVID-19 infection

In line with the results of our study, the results of other studies show that severe disease occurred in 18% of the pregnant woman (26). But, in a prospective cohort study, Pierce-Williams et al. reported, that 69% of pregnant women had severe diseases, and 31% had critical diseases (24). In a meta-analysis study, severe COVID-19 was reported in 11% of case reports/series and seven percent of observational studies (27). Presumably, the different prevalence severity of disease in the studies is related to the screening and hospitalization policies of the patients in each area and the characteristics of the study populations. Pregnant women with symptoms of the higher severe stage of the disease were hospitalized due to the high prevalence of the severe disease and the limited facilities.

In our study, women with severe and critical diseases were significantly older than pregnant women with mild and moderate diseases. About 32.6% of the women with severe diseases and more than 22% of women with critical diseases were over 35 years old. Other studies have reported increasing maternal age is associated with the severity of disease (24).

Our analysis showed that women with severe and critical disease significantly had higher BMI than pregnant women with mild and moderate disease. Other studies have reported that overweight and obesity in pregnant women are risk factors for increased morbidity, maternal death, and severity of COVID-19 disease in pregnancy (26, 28, 29). Also, based on a report by a systematic review, obesity is an independent predictor of the severity of COVID-19 (30).

In our study, 17.4% overall (32.6 % in the severe disease and 44.4 % in the critical stage) were Afghan. The findings of our study showed that the severity of the disease has a significant relationship with ethnicity. Other studies reported that more than fifty percent of pregnant women were from black or other ethnicities (31). Due to COVID-19, a high percentage of pregnant women of other ethnicities are hospitalized, it is of concern and, should be paid attention to these ethnic minorities because ethnic differences, health behaviors, and underlying diseases are risk factors for COVID-19 and increase the risk of the severity of disease in these groups (31, 32).

In our study, 61.3 percent of pregnant women in the third trimester, 27.1 percent in the second trimester, and 11. 6% were in the first trimester of pregnancy. Of this number, 72.1% of women with severe disease, and 77.8 % of women with the critical stage of disease were in the third trimester of pregnancy. Also, in the critical stage of the disease, 88.9% of women were multiparous. A significant relationship was observed between parity and the severity of the disease. Other studies have shown that most pregnant women hospitalized for complications of COVID-19 are in the third trimester of pregnancy (31, 33, 34). In a study by Qiancheng et al., 85% of pregnant women were in the third trimester of pregnancy (33). Physiological changes, including an elevated diaphragm and decreased residual volume, peak in the third trimester

of pregnancy (16). They may be considered a risk factor for severe pneumonia and are the causes of hospitalization of pregnant women.

Our findings show that more than half of pregnant women admitted with severe COVID-19 had underlying diseases. Also, evidence shows that women with underlying diseases increase the likelihood of the severity of the disease (24, 31) and the need for hospitalization in the intensive care unit(24).

Relationships between disease spectrum of COVID-19 infection and fetal and neonatal outcome

In general, our study showed that the severity of COVID-19, after adjusting the confounding variables, was significantly associated with fetal and neonatal outcomes including fetal distress, IUGR, preterm delivery, LBW, and APGAR scores at 1 minute <7.

Our results revealed that the severity of the disease is significantly associated with fetal distress and IUGR, and the severity of the disease is a predictor of fetal distress and IUGR. Based on a report by a systematic review, fetal distress was 16% (29). Contrary to the results of our study, Pierce-Williams et al, did not report a significant relationship between the severity of disease and IUGR (24).

Two stillbirths occurred in the critical stage of the disease. However, after controlling the intervening factors, stillbirth had no significant relationship with the severity of the disease. Based on a report by a systematic review, stillbirth was four percent (29). In a study by Knight et al., there were three stillbirths. They stated that the causes of these stillbirths were no complications due to maternal COVID-19, but these stillbirths were due to underlying fetal problems (31). Pierce-Williams et al. did not report any stillbirth (24).

The findings of our study show that the rate of spontaneous preterm birth was 16% overall (15 % in the severe disease and 55.6 % in the critical stage), which results show that, after adjusting for confounding variables, the severity of COVID-19 was not a predictor of spontaneous preterm birth. However, preterm birth was 43% overall (75 % in the severe disease and 100 % in the critical stage) and preterm birth was significantly associated with the severity of the disease. Contrary to our study, Du et al. reported that the severity of COVID-19 was significantly associated with premature rupture of membranes and spontaneous birth (35). Pierce-Williams et al. report that 59.4% of pregnant women with the severe and critical stage of disease had a preterm birth, that 88% of them were in critical disease and most preterm births were performed with cesarean section due to the maternal status (24). Another piece of evidence suggests that the severity of COVID-19 is associated with preterm birth (36). In one meta-analysis study, preterm delivery occurred in 16% of observational studies and 29.7% of case reports/series (27).

In our study, LBW was 11.9% in mild and moderate disease, 55% in severe disease, and 87.5% in the critical stage. The mean birth weight was 2962.6± 580.08 in the mild to moderate disease group, 2490.2±542.6 in the severe disease group, and 1881.1±717.7 in the critical disease group. The findings of our study showed that LBW is significantly associated with the severity of the disease.

This means birth weight in severe and critical COVID-19 was similar to the findings of the study by Pierce-Williams et al.; they reported that weight loss at birth in the severe and critical stage of COVID-19 is probably due to the complications of COVID-19 in the mother and preterm birth (24).

Vertical transmission occurred in only four (4.2%) pregnant women who delivered, one (5%) in severe disease, and 3(37.5%) in the critical stage. After adjusting for confounding variables vertical transmission is not significantly associated with the severity of COVID-19. Also, Alzamora et al. reported one vertical transmission that occurred in a pregnant woman was in the severe stage of the disease (36). In a systematic review, COVID-19 in the third trimester of pregnancy was linked to a low rate of vertical transmission (3.2%) (37). In a meta-analysis study, the risk of vertical transmission was reported to be low and was not affected by the severity of COVID-19 (27). Evidence indicates that there are numerous questions

regarding vertical transmission, including when it occurs and how it correlates with the severity of COVID-19. Further studies in this area are necessary.

Our results revealed that admission to NICU is significantly associated with the severity of COVID-19. In Pierce-Williams et al.'s study, over 83% of mothers with newborns in critical stages of the disease and 40% of infants born to mothers with severe diseases were admitted to the NICU, confirming the findings of our study (24). In a study by Knight et al., 25 percent of infants were admitted to the intensive care unit (31). However, after adjusting for confounding variables such as maternal age, BMI, ethnicity, trimester of pregnancy, parity, and underlying diseases, the severity of COVID-19 was not a predictor of admission to NICU. Also, Savasi et al. report that 12% of neonate mothers with COVID-19 were admitted to NICU, but not a significant relationship between the severity of COVID-19 and hospitalization in NICU (26). The results indicate that hospitalization in the NICU is related to preterm birth and other confounding factors.

The findings of our study showed that the rate of Apgar scores at 1-minutes<7 was 10.5 % overall (six percent in mild and moderate disease, ten percent in severe disease, and 50% in the critical stage). Also, the rate of the Apgar scores at five min<7 was 4.2 % overall (1.5 percent in mild and moderate disease, 5 percent in severe disease, and 25% in the critical stage). However, after adjusting for confounding variables, the severity of COVID-19 was not a predictor of Apgar scores at 5 minutes<7. Also, in other studies, no significant relationship was reported between severity of disease and low Apgar score at 1&5 min (26, 27, 29).

In our study, there were no neonatal sepsis and neonatal deaths. The study of Pierce-Williams et al. did not report cases of neonatal death (24). In one meta-analysis study (27), no neonate deaths occurred in observational studies. In case reports/series, two neonate deaths occurred in mothers with severe diseases who were hospitalized in the ICU. Knight et al. reported 1 (2%) neonate deaths (31).

Limitations

One of the strengths of the present study, Forghani Hospital, was the only general hospital that pregnant women were referred to this hospital for COVID-19 from all over Qom province, from each ethnicity, race, and economic level. Therefore, the results can be generalized to the entire research community. One of the weaknesses of the present study is that due to the cross-sectional nature of the study, the cause-and-effect relationship cannot be proven. Since the patients with COVID-19 disease were divided into three groups of critical stage, severe and mild based on the severity of the disease, the number of samples in the critical stage group was small. As a result, wide confidence intervals were obtained in most of the results. It seems that this study may need a larger sample size. Also, in this study, the medical records of all pregnant women who were referred due to COVID-19 are not available. Also, some variables were not reported. In conclusion, our analytical cross-sectional study provided valuable information about the severity of COVID-19 in pregnancy, and the results showed that their neonates were exposed to higher potential risks such as fetal distress, IUGR, preterm delivery, LBW, and Apgar scores at 1 minute <7 than women with mild to moderate disease..

Competing interests

The authors declare that they have no competing interests.

Funding

This study was supported by the Qom University of Medical Sciences (IR.MUQ.REC.1399.152). And no funding has been received from other organizations .The funding agencies did not participate in the study design, data collection, data analysis, or writing of the report. The final version was approved by all authors.

Acknowledgments

The researchers would like to sincerely thank the Research Deputy, Midwifery and Reproductive Health professors of the Qom Department of Nursing and

Midwifery, for their unwavering efforts and assistance in writing, editing, and conducting this study.

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