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Relationship between coronavirus disease 2019 in pregnancy and maternal and fetal outcomes: Retrospective analytical cohort study

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ABSTRACT

Objective: Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has caused many deaths and complications worldwide. However, limited data are available about COVID-19 during pregnancy. This study aimed to assess the epidemiological and clinical features of COVID-19, and the adverse maternal and fetal outcomes.

Design: This retrospective analytical cohort study was conducted on all pregnant women with confirmed COVID-19 at Nekouei-Hedayati-Forghani Hospital in Qom, Iran from 15 March 2020 to 15 November 2020. For the same period, 165 pregnant women who did not have COVID-19 were selected at random and included in this study. All epidemiological and clinical features were collected from the medical records of the participants. A logistic regression model was used to determine associations between COVID-19 in pregnancy and maternal and fetal outcomes.

Findings: The most common symptoms reported by pregnant women with COVID-19 were shortness of breath (60.9%), dry cough (59%) and fever (42.9%). After adjustment for potential confounding factors, COVID-19 in pregnancy was associated with a significantly higher risk of admission to the intensive care unit (ICU) [odds ratio (OR) 6.16, 95% confidence interval (CI) 1.23–31], caesarean section (OR 0.45, 95 CI 0.25–1.03), preterm birth (OR 3.01, 95% CI 1.4–6.54), fetal distress (OR 5.7, 95% CI 2.13–15.59) and admission to the neonatal intensive care unit (NICU) (OR 3.04, 95% CI 1.21–7.70).

Key conclusions: COVID-19 is associated with adverse maternal and fetal outcomes, including ICU admission, caesarean section, fetal distress, preterm birth and NICU admission.

Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), was declared a pandemic and a global health emergency in March 2020 (Huang et al., 2020; World Health Organization, 2020a). COVID-19 is a highly infectious disease (Huang et al., 2020; N. Zhu et al., 2020), and high numbers of deaths and complications have been reported (Allotey et al., 2020). The risk of COVID-19 among pregnancy women is the same as in the general population (Docherty et al., 2020). However, physiological changes (e.g. reduction of functional residual volume, oedema of respiratory tract mucosa) and immunological changes during pregnancy can increase susceptibility to viral infections and cause more severe consequences (Akhtar et al., 2020). Evidence for similar viral diseases (SARS and Middle East respiratory syndrome) shows that pregnant

women and their infants are at higher risk of mortality (Alfaraj et al., 2019; Mullins et al., 2020; Wong et al., 2004). Also, there is evidence that COVID-19 is more severe in late pregnancy (Knight et al., 2020; Mullins et al., 2020). Due to concerns about the effect of COVID-19 on maternal–fetal outcomes and during the postpartum period, pregnant women are considered as a high-risk group (Allotey et al., 2020). The rates of adverse pregnancy outcomes such as intrauterine fetal distress, preterm labour, caesarean section for both maternal and fetal reasons, fetal growth restriction and stillbirth have been reported to be higher in pregnant women with COVID-19 (Allotey et al., 2020; Chen et al., 2020; Knight et al., 2020; H. Zhu et al., 2020; N. Zhu et al., 2020), and 94% of preterm births had iatrogenic causes in pregnant women with COVID-19 (Allotey et al., 2020). Also, Mendoza and Garcia-Ruiz (2020) reported that the clinical signs of a pre-eclampsia-like syndrome could be present in some pregnant women with severe COVID-19; similarly, other risk

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Table 1
Comparison baseline characteristics in pregnant women with and without coronavirus disease 2019 (COVID-19).

	COVID-19 (n=133) (%)	No COVID-19 (n=165) (%)	p-value
Age, mean (SD), years ^a	29.4 (5.8)	30.7 (6.3)	0.06
Body mass index			
Normal	117 (88)	134 (81.2)	0.19
Overweight	7 (5.3)	18 (10.9)	
Obese	9 (6.8)	13 (7.9)	
Other minority ethnic group (all)			
Iran	109 (82.0)	156 (94.5)	0.000
Afghan	24 (18.0)	9 (5.5)	
Parity			
Nulliparous	31 (23.3)	47 (28.5)	0.31
Multiparous	102 (76.7)	118 (71.5)	
Trimester of pregnancy			
First	17 (12.8)	3 (1.8)	0.000
Second	37 (27.8)	14 (8.5)	
Third	79 (59.4)	148 (89.7)	
Pregnancy			
Twins	6 (4.5)	11 (6.7)	0.41
Singleton	127 (95.5)	154 (93.3)	
Pre-existing medical problems			
No medical problems	88 (65.9)	127 (77)	0.17
Asthma	2 (1.5)	0 (0)	
Hypertension	13 (9.8)	10 (6.1)	
Gestational diabetes	15 (11.4)	18 (10.9)	
Diabetes	3 (2.3)	4 (2.4)	
Liver disease	2 (1.5)	0 (0)	
Anaemia	4 (3)	1 (0.6)	
Renal disease	1 (0.8)	0 (0)	
Severe pre-eclampsia	2 (1.5)	1 (0.6)	
GDM and hypertension	3 (2.3)	4 (2.4)	

GDM, gestational diabetes mellitus; SD, standard deviation.

^a Student's *t*-test.

factors such as ethnicity, pre-existing diseases associated with severe COVID-19, and these adverse pregnancy outcomes have not been established to date (Allotey et al., 2020). Studies have investigated epidemiological characteristics; clinical, laboratory and radiological features; therapeutic features and clinical outcomes in adults with COVID-19. However, clinical features and the potential for vertical transmission of COVID-19 remain unknown in pregnant women (Huang et al., 2020). To date, the majority of retrospective and prospective cohort studies have only investigated and reported pregnancy and fetal outcomes in pregnant women with COVID-19, and have not compared the findings with outcomes in pregnant women without COVID-19 (Ayed et al., 2020; Du et al., 2021; Knight et al., 2020; Pierce-Williams et al., 2020; Yin et al., 2020; Yu et al., 2020; Zhou et al., 2020). The World Health Organization (WHO) has recommended that pregnancy and fetal outcomes of pregnant women with COVID-19 should be compared with those of pregnant women without COVID-19 to determine if COVID-19 during pregnancy increases the risk of adverse pregnancy or fetal outcomes (World Health Organization, 2020b).

As such, this study aimed to assess the epidemiological and clinical features of COVID-19, and the adverse maternal and fetal outcomes.

Methods

Design and participants

An analytical and retrospective cohort study was conducted on 312 pregnant women (5–42 weeks of gestation) hospitalized due to COVID-19 at Nekouei-Hedayati-Forghani Hospital in Qom, Iran between 15 March 2020 to 15 November 2020. Nekouei-Hedayati-Forghani Hospital, a tertiary referral hospital, was designated for the management of pregnant women with COVID-19 and neonates born to infected mothers in Qom, Iran. Among 312 hospitalized pregnant women with COVID-19 confirmed by real-time reverse transcriptase polymerase chain reaction (RT-PCR) assay (nasopharyngeal swab specimens) or multiple mottling

and ground-glass opacity on computed tomography (CT) scan or both, the medical records of 133 pregnant women were available and included in this study.

Over the same period, approximately 1120 pregnant women without COVID-19 were hospitalized due to other complications of pregnancy and childbirth. One hundred and sixty five of these pregnant women without COVID-19 were selected at random and included in this study.

Data collection

All clinical features, and laboratory and radiographic data were collected from the medical records of pregnant women from the day of admission to discharge. A reproductive health and obstetrics specialist collected the data. The following information was collected: epidemiological and clinical manifestations, symptoms, need for respiratory support and intensive care unit (ICU) admission, antibiotic and viral therapies associated with COVID-19, chest CT and pre-existing diseases (e.g. gestational diabetes, chronic diabetes, chronic hypertension and pre-eclampsia, kidney disease, liver cancer). In addition, information on the following demographic and obstetric characteristics was collected: maternal age, body mass index, ethnicity, gestational age, parity, twins and abortion. In terms of fetal outcomes, information about preterm birth (<37 weeks of pregnancy), spontaneous preterm birth, mode of birth, meconium excretion, low birth weight (<2500 g), Apgar score at 1 and 5 min, vertical transmission, neonatal intensive care unit (NICU) admission, fetal distress, stillbirth and neonatal death was collected.

Maternal outcomes such as acute respiratory distress syndrome (ARDS), acute renal failure, acute respiratory injury, ventilator-associated pneumonia, ICU admission and maternal mortality were assessed from the medical records of pregnant women. Also, laboratory findings such as lymphopenia, leukopenia, thrombocytopenia, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and white blood cell count were collected.

Table 2

Clinical manifestations, laboratory findings, maternal and fetal outcomes, and treatment of pregnant woman with coronavirus disease 2019.

Clinical manifestations (n=133) (%)	
Shortness of breath	81 (60.9)
Dry cough	79 (59)
Fever	57 (42.9)
Myalgia	38 (28.6)
Headache	33 (24.8)
Weakness	23 (17.3)
Pharyngalgia	23 (17.3)
Tachycardia	23 (17.3)
Chills	18 (13.5)
Vomiting	16 (12)
Nausea	17 (12.8)
Dizziness	14 (10.5)
Expectoration	12 (9.1)
Diarrhoea	12 (9.1)
Rhinorrhoea	9 (6.8)
No smell	5 (3.8)
Haemoptysis	3 (2.3)
Hospital stay (days), mean (SD)	
Laboratory findings	4.4 (3.6)
White cell count	
Decreased	8 (6)
Lymphopenia	
Yes	15 (11.3)
Thrombocytopenia	
Yes	24 (18)
Elevated ALT (>45 U/l)	
Yes	26 (19.5)
Elevated AST (>35 U/l)	
Yes	22 (16.5)
C-reactive protein (mg/l; normal range 0.0–5.0)	
Increased	103 (88.8)
Erythrocyte sedimentation rate (mm/h; normal range 0.0–15.0)	
Increased	108 (95.5)
SARS-CoV-2 quantitative RT-PCR test result	
Positive	105 (85.4)
Negative	3 (2.4)
CT findings	
Ground-glass opacity	34 (27.6)
Maternal outcomes	
ARDS	
Acute renal injury	1 (1.2)
Acute respiratory injury	11 (8.9)
Ventilator-associated pneumonia	15 (11.3)
ICU admission	15 (11.3)
Maternal death	4 (3.3)
NICU admission	18 (34.0)
Vertical transmission	4 (3.7)
Stillbirth	2 (1.6)
Treatment	
Antibiotic	68 (55.3)
Antiviral	15 (12.2)

SD, standard deviation; ALT, alanine aminotransferase; AST, aspartate aminotransferase; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; CT, computed tomography; ARDS, adult respiratory distress syndrome; RT-PCR, reverse transcriptase polymerase chain reaction; ICU, intensive care unit; NICU, neonatal intensive care unit.

The sample size in this study, according to $\alpha = 0.05$, $\beta = 0.1$ in the Gigi table and based on a similar research paper (Yin et al., 2020), was at least 40 patients with COVID-19.

Data analysis

A descriptive statistical analysis was performed using absolute and relative frequencies for qualitative variables, and mean and standard deviation for quantitative variables to describe the characteristics of the study population. Relationships between qualitative and quantitative variables were analysed using Chi-squared test and Student's *t*-test, respectively. A logistic regression model was used to determine associations between COVID-19 in pregnancy and maternal and fetal outcomes.

Associations were adjusted for confounding factors such as ethnicity and trimester of pregnancy. Quantitative data were also analysed using linear regression. SPSS 22 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. $p < 0.05$ was considered to indicate significance.

Ethical-legal considerations

This study was approved by the Ethics Committee of Qom University of Medical Sciences (No. IR.MUQ.REC.1399.152) and was conducted in accordance with the principles of the Declaration of Helsinki.

Results

Medical records were available for 133 of the 312 pregnant women with confirmed COVID-19, so these cases were included in this study. For the same period, 165 pregnant women without COVID-19 were selected at random and included in this study for comparison of maternal and fetal outcomes of pregnant women with COVID-19.

Demographics and baseline characteristics

The mean age of pregnant women with COVID-19 was 29.4 [standard deviation (SD) 5.8] years, and the mean age of pregnant women without COVID-19 was 30.7 (SD 6.3) years; this difference was not significant ($p > 0.05$).

In addition, no significant differences were found between the two groups of pregnant women in terms of body mass index, parity, twins and history of pre-existing diseases ($p > 0.05$). Significant differences between the two groups were found in terms of trimester of pregnancy and ethnicity ($p = 0.001$) (Table 1).

Clinical manifestations of COVID-19 during pregnancy

The most common symptoms reported by pregnant women with COVID-19 were shortness of breath (60.9%), dry cough (59%) and fever (42.9%) (Table 2).

Of the pregnant women with COVID-19, one (1.2%) had acute renal injury, 25 (20.3%) had ARDS, 11 (8.9%) had acute respiratory injury, 15 (11.3%) had invasive ventilation-associated pneumonia, 15 (11.3%) were admitted to ICU, four (3.3%) mothers died, 18 (34 %) neonates were admitted to NICU, vertical transmission occurred in four (3.7%) neonates, and two (1.6%) stillbirths occurred (Table 2).

Laboratory and radiological findings

In this study, laboratory and radiological findings showed that 11.3% of pregnant women with COVID-19 had lymphopenia and 18% had thrombocytopenia. ALT and AST were elevated in 19.5% and 16.5% cases, respectively. CRP and ESR were elevated in 88.8% and 95.5% of cases, respectively. Typical changes on chest CT with multiple patchy ground-glass shadows were observed in 34 (27.6%) pregnant women with COVID-19, and 105 (85.4%) pregnant women with COVID-19 had positive RT-PCR.

Treatments

Fifteen (12.2%) pregnant women with COVID-19 received antiviral drugs, and 68 (55.3%) received prophylactic antibiotics (Table 2).

Relationships between antenatal COVID-19 and maternal outcomes

Of all the pregnant women with COVID-19, 53 (39.8%) had given birth: 20 (37.7%) woman had a vaginal birth and 33 (62.2%) woman had a caesarean section. Of the caesarean sections, 22.6% were performed due to complications of COVID-19 in the mother, 17.0% were

Table 3
Comparison of pregnancy and fetal outcomes in pregnant women with and without coronavirus disease 2019 (COVID-19).

	COVID-19	No COVID-19	p-value
Mode of birth	(n=53) (%)	(n=135) (%)	
Normal vaginal delivery	20 (37.7)	47 (34.6)	0.000
Caesarean section due to other indications	9 (17.1)	70 (51.9)	
Caesarean section due to complications of COVID-19	12 (22.6)	0 (0.0)	
Caesarean section due to fetal distress	12 (22.6)	18 (13.3)	
Postpartum haemorrhage	(n=53) (%)	(n=135) (%)	
Yes	2 (3.8)	1 (0.7)	0.1
No	51 (96.2)	134 (99.3)	
ICU admission	(n=133) (%)	(n=165) (%)	
Yes	15 (11.3)	2 (1.2)	0.000
No	118 (88.7)	163 (98.8)	
Maternal mortality	(n=133) (%)	(n=165) (%)	
Yes	4 (3.0)	0 (0.0)	0.03
No	129 (97.0)	165 (100)	
Fetal distress	(n=53) (%)	(n=135) (%)	
Yes	20 (37.7)	7 (5.2)	0.000
No	33 (62.3)	128 (94.8)	
Spontaneous preterm birth	(n=53) (%)	(n=135) (%)	
Yes	7 (13.2)	10 (7.4)	0.2
No	46 (86.8)	125 (92.6)	
Preterm birth <37 weeks	(n=53) (%)	(n=135) (%)	
Yes	25 (47.2)	18 (13.3)	0.000
No	28 (52.8)	117 (86.7)	
Low birth weight (<2500 g)			
Yes	16 (30.2)	20 (14.8)	0.02
No	37 (69.8)	115 (85.2)	
Meconium excretion	(n=53) (%)	(n=135) (%)	
Yes	4 (7.5)	2 (1.5)	0.05
No	49 (92.5)	133 (98.5)	
NICU admission	(n=53) (%)	(n=135) (%)	
Yes	18 (34.0)	10 (7.4)	0.000
No	35 (66.0)	125 (92.6)	
Apgar score at 1 min, mean (SD) ^a	8.2 (1.7)	8.8 (0.7)	0.003
Apgar score at 5 min, mean (SD)	9.1 (1.5)	9.8 (0.8)	0.000

ICU, intensive care unit; NICU, neonatal intensive care unit; SD, standard deviation.

^a Student's *t*-test.

Table 4
Logistic regression model testing the association between antenatal coronavirus disease 2019 and pregnancy outcomes.

	Crude OR	p-value	AdjOR ^a	p-value	95% CI
Caesarean section	0.66	0.22	0.45	0.04	0.20–1.03
Postpartum haemorrhage	2.60	0.44	3.44	0.35	0.26–47.40
ICU admission	10.23	0.002	6.16	0.03	1.23–31
Maternal mortality	1.10	1.10	0.09	0.15	0.01–1.35

CI, confidence interval; OR, odds ratio; AdjOR, adjusted OR; ICU, intensive care unit.

^a Adjusted for ethnic group and trimester of pregnancy.

performed due to recurrent caesarean section, and 22.6% were performed due to fetal distress (Table 3).

Using Chi-squared test, the results showed that caesarean section, ICU admission and maternal death were significantly associated with COVID-19 ($p < 0.05$) (Table 3).

Ethnicity and trimester of pregnancy were considered as potential confounding factors, so all models were adjusted accordingly. After adjustment, COVID-19 in pregnancy was associated with a significantly higher risk of caesarean section [odds ratio (OR) 0.45, 95% confidence interval (CI) 0.20–1.03] and ICU admission (OR 6.16, 95% CI 1.23–31). Maternal mortality rate (95% CI 0.4–2.7%) and postpartum haemorrhage (OR 3.64, 95% CI 0.26–47.4) were higher in pregnant women with COVID-19, but no significant association was found between COVID-19 and maternal mortality and postpartum haemorrhage (Table 4).

Relationships between antenatal COVID-19 and fetal outcomes

The results of Chi-squared tests showed that fetal distress, preterm birth, low birth weight, meconium excretion and NICU admission were

significantly associated with COVID-19 ($p < 0.05$). Also, the results of an independent *t*-test showed that the Apgar scores at 1 and 5 min differed significantly between neonates born to pregnant women with COVID-19 and neonates born to pregnant women without COVID-19 ($p < 0.05$) (Table 3).

Ethnicity and trimester of pregnancy were considered as potential confounding factors, and so all models were adjusted accordingly. Following adjustment, COVID-19 in pregnancy was associated with a significantly higher risk of preterm birth (OR 3.01, 95% CI 1.4–6.54), fetal distress (OR 5.7, 95% CI 2.13–15.59) and NICU admission (OR 3.04, 95% CI 1.21–7.70). No significant relationship was found between COVID-19 in pregnancy and meconium excretion and low birth weight ($p > 0.05$) (Table 5).

Linear regression analysis was used to investigate the relationship between COVID-19 in pregnancy and Apgar scores. The results showed that COVID-19 in pregnancy was not significantly associated with low Apgar scores at 1 and 5 min ($p > 0.05$) (Table 6).

Discussion

This study assessed epidemiological and clinical features and adverse maternal and fetal outcomes associated with COVID-19. There were no significant differences in terms of maternal age, body mass index, parity, twins and underlying diseases between pregnant women with COVID-19 and pregnant women without COVID-19. However, the two groups differed significantly in terms of trimester of pregnancy and ethnicity: 59.4% of pregnant women with COVID-19 were in the third trimester and 27.8% were in the second trimester. In common with previous reports, most pregnant women with COVID-19 admitted to hospital were in the third trimester (Knight et al., 2020; Pierce-Williams et al., 2020). An increase in hospital admissions in the third trimester has also been reported in the context of influenza (Fell et al., 2017). Increased oxygen consumption, reduced functional residual capacity in pregnancy (Stephens et al., 2020), and excessive uterine distension in the third trimester may further disturb pulmonary function, and are associated with severe disease (Berghella and Hughes 2020). Therefore, these factors probably increase the admission of pregnant women with COVID-19 in the third trimester.

In terms of ethnicity, 18% of pregnant women with COVID-19 were Afghan. Other studies have reported that racial and ethnic differences increase the risk of COVID-19 and its severity (Delahoy et al., 2020; Knight et al., 2020; Zambrano et al., 2020).

Trimester of pregnancy and ethnicity were considered as potential confounding factors in this study, and adjustments were made in the data analysis.

In this study, the most common clinical symptoms in pregnant women admitted to hospital with COVID-19 were shortness of breath (60.9%), dry cough (59%) and fever (42.9%). In a systematic review, the most common symptoms of pregnant women with COVID-19 were fever (40%) and cough (39%) (Allotey et al., 2020). Another systematic review reported that fever and cough were the most common symptoms in pregnant women with COVID-19 (Elshafeey et al., 2020). Despite the findings of other studies, shortness of breath was one of the most common symptoms in the present study; this may be due to overlap with symptoms of normal pregnancy. Another systematic review reported that some of the clinical symptoms of COVID-19 overlap with symptoms of normal pregnancy (shortness of breath, nasal congestion, nausea/vomiting), and this should be considered in the assessment of pregnant women with COVID-19 (Berghella and Hughes 2020).

In this study, laboratory findings showed that 11.3% of pregnant women with COVID-19 had lymphopenia. This is in agreement with previous studies (Ayed et al., 2020; Shi et al., 2020; Smith and Seo 2020). A systematic review reported that lymphopenia was the most common abnormal laboratory finding (Diriba et al., 2020).

Elevated ALT and AST were seen in 19.5% and 16.5% of pregnant women with COVID-19, respectively, in this study. In addition, a retrospective study found the likelihood of increased concentrations of ALT or AST as one of the clinical manifestations of COVID-19 (Chen et al., 2020). Consistent with the results of the present study, a systematic re-

view reported elevated ALT and AST with prevalence rates ranging from 16.8% to 18.8% (Diriba et al., 2020).

In the present study, 88.8% of pregnant women with COVID-19 had elevated CRP and 95.5% had elevated ESR. Similarly, other studies have reported elevated ESR and CRP in pregnant women with COVID-19 (Allotey et al., 2020; Shi et al., 2020).

Relationship between COVID-19 and maternal outcome

After adjustment for trimester of pregnancy and ethnicity, regression analysis showed that the rate of caesarean section in pregnant women with COVID-19 was significantly higher compared with pregnant women without COVID-19. Systematic reviews have reported that the caesarean section rate was higher in pregnant women with COVID-19 (Allotey et al., 2020; Di Mascio et al., 2020; Elshafeey et al., 2020; Juan and Gil 2020), but it is not clear how many caesarean sections were performed due to COVID-19 complications (Knight et al., 2020). In the present study, comparison of pregnant women with COVID-19 with pregnant women without COVID-19 showed that 22.6% of caesarean sections were performed due to complications of COVID-19.

In this study, the results showed that ICU admission was six times higher in pregnant women with COVID-19. Other studies have reported that ICU admission and need for invasive ventilation are higher in pregnant women compared with non-pregnant women, particularly pregnant women with pre-existing diseases (Allotey et al., 2020; Delahoy et al., 2020).

In this study, four pregnant women with COVID-19 died. Chi-squared test showed a significant relationship between maternal death and COVID-19. However, after adjusting for trimester of pregnancy and ethnicity, regression analysis showed that the relationship between COVID-19 and maternal death was not significant. The prevalence of maternal mortality differed between studies (Elshafeey et al., 2020; Hantoushzadeh et al., 2020; Knight et al., 2020; Pierce-Williams et al., 2020). Pierce-Williams et al. (2020) found no maternal deaths due to COVID-19, and Elshafeey et al. (2020) reported one death. A prospective cohort study reported five deaths (Knight et al., 2020), and a retrospective case series study reported a high mortality rate in women with severe COVID-19 (seven of nine cases) (Hantoushzadeh et al., 2020). The factors most likely to affect maternal mortality are disease severity and maternal age.

In the present study, 3.8% of pregnant women with COVID-19 experienced postpartum haemorrhage; this did not differ significantly from pregnant women without COVID-19. A prospective cohort study found that postpartum haemorrhage was 9% overall in women with severe and critical disease, and did not observe a significant difference compared with pregnant women with mild disease (Pierce-Williams et al., 2020). Another study did not report an increased risk of postpartum haemorrhage in pregnant women with COVID-19 (Zhang et al., 2020). These inconsistent results may be due to selection bias due to the small sample sizes. The effects of COVID-19 in pregnancy require further research.

Table 5

Logistic regression model testing the association between antenatal coronavirus disease 2019 and fetal outcomes.

	Crude OR	p-value	AdjOR ^a	p-value	95% CI
Fetal distress	4.44	0.001	5.76	0.001	2.13–15.59
Preterm birth <37 weeks	2.07	0.03	3.01	0.005	1.40–6.54
Low birth weight	1.16	0.68	0.92	0.8	0.40–2.16
Meconium	2.60	0.27	5.86	0.05	0.93–36.90
NICU admission	2.77	0.01	3.04	0.01	1.21–7.70

CI, confidence interval; OR, odds ratio; AdjOR, adjusted OR; NICU, neonatal intensive care unit.

^a Adjusted for ethnic group and trimester of pregnancy.

Table 6
Linear regression testing the association between antenatal coronavirus disease 2019 and Apgar score

	Univariate			Multivariate			
	β	S.E.	p-value	β	S.E.	p-value	95% CI
Apgar score at 1 min	-0.54	0.22	0.000	-0.27	0.21	0.19	-0.69-0.14
Apgar score at 5 min	-0.59	0.22	0.009	-0.36	0.20	0.08	-0.77-0.05

CI, confidence interval.

Relationship between COVID-19 and fetal outcomes

In the first 12 h after birth, the PCR tests of four neonates born to pregnant women with COVID-19 were positive; two of these were stillbirths. The prevalence of vertical transmission was 3.7%. A systematic review reported that 3.2% of neonates tested positive on PCR (Kotlyar et al., 2020). In other studies, the PCR test was negative and no cases of vertical transmission occurred (Knight et al., 2020; Pierce-Williams et al., 2020). In the present study, all cases of vertical transmission occurred in mothers who had critical disease or mothers who died in the third trimester of pregnancy. Wu et al. (2020) reported four cases of vertical transmission that occurred in mothers with severe COVID-19. Penfield et al. (2020) reported that three of 11 swabs sent from placental samples were positive for COVID-19, and all positive cases occurred in women with severe COVID-19. Kotlyar et al. (2020) reported that most cases of vertical transmission occurred in the third trimester of pregnancy. The differing results show that more research is needed regarding the association between vertical transmission and disease severity and trimester of pregnancy.

The results of Chi-squared tests and independent t-tests showed that fetal outcomes such as fetal distress, preterm birth, low birth weight, meconium excretion, NICU admission and Apgar score at 1 and 5 min were significantly associated with COVID-19. However, after adjusting for trimester of pregnancy and ethnicity, regression analysis showed that fetal distress, preterm birth and NICU admission were significantly higher in pregnant women with COVID-19.

In this study, the prevalence of fetal distress among pregnant women with COVID-19 was significantly higher compared with pregnant women without COVID-19, and 37.7% of pregnant women with COVID-19 had fetal distress, which may be related to the higher caesarean section rate (Du et al., 2021). In other studies, the risk of fetal distress among pregnant women with COVID-19 was 14% higher compared with pregnant women before the pandemic (Du et al., 2021). Also, Elshafeey et al. (2020) reported that the prevalence of fetal distress in pregnant women with COVID-19 was 7.8%, and the low incidence of fetal distress was due to the fact that 95% of pregnant women had mild COVID-19.

This study found that preterm birth was significantly higher in pregnant women with COVID-19 compared with pregnant women without COVID-19, and 47.2% of pregnant women with COVID-19 had a preterm birth. In a systematic review, preterm birth was higher among pregnant women with COVID-19 compared with those without COVID-19 (Allotey et al., 2020). It has been reported that most preterm births have occurred due to maternal indications and in the third trimester (Knight et al., 2020), and Pierce-Williams et al. (2020) found that complications such as preterm labour were common in mothers with severe COVID-19. In the present study, the spontaneous preterm birth rate was not significantly associated with COVID-19, in agreement with other studies which reported that the spontaneous preterm birth rate was similar to that observed in the pre-pandemic period (Allotey et al., 2020; Yang et al., 2020).

In the present study, low birth weight was not significantly associated with COVID-19 after controlling for confounding factors. Yang et al. (2020) did not report a significant difference between pregnant women with COVID-19 and pregnant women without COVID-19 in terms of low birth weight. Therefore, the low birth weight was probably

due to preterm birth due to complications of COVID-19 in the mother. However, Pierce-Williams et al. (2020) found that birth weight differed significantly between mothers with severe COVID-19 and mothers with critical COVID-19.

The results of the present study show that 7.5% of neonates born to pregnant women with COVID-19 had meconium excretion, with a higher risk of NICU admission (OR 5.86) compared with neonates born to mothers without COVID-19. After adjustment for confounding factors, no significant relationship was found between meconium excretion and COVID-19 in pregnancy. Consistent with the present study, Zhang et al. (2020) did not find increased risk of meconium-stained amniotic fluid in pregnant women with COVID-19.

The present study shows that 34% of neonates born to pregnant women with COVID-19 were admitted to an NICU, and the risk of NICU admission was higher among neonates born to mothers with COVID-19 compared with neonates born to mothers without COVID-19 (OR 3.04). Consistent with the results of the present study, Pierce-Williams et al. (2020) reported that 40% of infants of mothers with COVID-19 were admitted to an NICU. A systematic review showed that the risk of NICU admission was higher among neonates of pregnant women with COVID-19 compared with neonates of pregnant women without COVID-19 (Allotey et al., 2020).

The present study found that the Apgar scores at 1 and 5 min of neonates of pregnant women with COVID-19 were not significantly lower compared with neonates of pregnant women without COVID-19. Another study reported that neonates of mothers with severe COVID-19 had lower Apgar scores compared with other neonates (Pierce-Williams et al., 2020). Other studies reported that neonates of mothers with mild and moderate COVID-19 had normal Apgar scores (Wu et al., 2020; Yu et al., 2020).

The strengths of the present study were selection of a control group, and comparison of maternal and fetal outcomes between the two groups. Using a set of data based on the obstetric and laboratory characteristics of two groups (pregnant women with and without COVID-19) enabled the evaluation of relationships between variables. It also enabled maternal and fetal outcomes to be examined by controlling for potential confounding variables, so the authors were able to investigate the impact of COVID-19 on pregnancy outcomes independent of the effect of gestational age, ethnicity, underlying diseases and multiple pregnancies. Also, all pregnant women with COVID-19 in Qom were referred to a centre according to the recommendations of Qom University of Medical Sciences, and the results are comparable for the entire population of the region. Limitations of this study include its retrospective design, as some variables were not available.

Conclusion

The results show that the most common clinical symptoms of COVID-19 in pregnancy were shortness of breath, dry cough and fever. Also, COVID-19 was associated with increased caesarean section, ICU admission, fetal distress, preterm birth and NICU admission. However, the retrospective nature of this study limits the conclusions. The authors believe that the findings of this study help to explain the clinical characteristics of COVID-19 in pregnancy, and its impacts on maternal and fetal outcomes. Despite this, further research is required to evaluate long-term outcomes.

Ethical approval

The study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the Ethics Committee of Qom University of Medical Sciences (No. IR.MUQ.REC. 1399.152).

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Declaration of Competing Interest

The authors declare that there are no conflicts of interest

CRediT authorship contribution statement

Zahra Alipour: Methodology, Resources, Formal analysis, Data curation, Writing – review & editing, Project administration, Funding acquisition. **Parisa Samadi:** Writing – review & editing. **Narges Eskandari:** Methodology, Writing – review & editing. **Maryam Ghaedrahmati:** Writing – review & editing, Data curation. **Mostafa Vahedian:** Formal analysis, Writing – review & editing. **Zohre Khalajinia:** Writing – review & editing. **Ali Mastanijahroodi:** Data curation.

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