Journal of Obstetrics, Gynecology and Cancer Research | ISSN: 2476-5848

Comparison of Obstetric and Neonatal Outcomes in Pregnant Women with and Without COVID-19 Infection: A Single-Center Prospective Cohort Study

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Article Info

10.30699/jogcr.9.5.542

Received: 2024/03/20;
Accepted: 2024/07/10;
Published Online: 18 Aug 2024;

Use your device to scan and read the article online

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ABSTRACT

Background & Objective: The study aims to determine the adverse effects of a mild COVID-19 infection on maternal and neonatal outcomes in pregnant women living in the eastern part of Tehran.

Materials & Methods: In this prospective cohort study, we followed two groups of pregnant women until term and their pregnancy and neonatal outcomes. RT-PCR (reverse transcriptase polymerase chain reaction) positive tests of nasopharyngeal swabs were confirmed in one group, where at least three signs and symptoms associated with COVID-19, and/or chest CT scans identified highly specific findings for the disease were present. The control group is composed of healthy pregnant women tested negative for COVID-19.

Results: The study included 319 pregnant women (108 with mild COVID-19 infection and 211 healthy). A higher percentage of mothers with mild COVID-19 infection had preterm births (47.9% vs. 30%, p=0.007), and their neonates required hospitalization more often (45.8% vs. 22.6%, p<0.001). PTB was positively associated with maternal hypertension (relative risk (RR): 5.40), mild COVID-19 infection (RR: 2.05), and older age (RR: 1.05). Among the risk factors for neonatal hospitalization, PTB (RR: 5.94), maternal hypertension (RR: 2.74), and mild COVID-19 infection during pregnancy (RR: 2.57) were significant.

Conclusion: The outcomes of pregnancy are significantly impacted by maternal infection with COVID-19, even if it is mild. Preterm births are more likely to happen in mothers with mild COVID-19 infection, and neonates need more hospitalizations.

Keywords: COVID-19, Premature Birth, Newborn, Pregnancy Outcome

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Introduction

In early 2020, the World Health Organization (WHO) declared the COVID-19 outbreak a public health challenge and a pandemic **(1)**. As a result of changes in their respiratory, cardiovascular, and immune systems, pregnant women are more susceptible to infection **(2)**. Studies comparing pregnant women with nonpregnant women showed that pregnant women with COVID-19 infections are more likely to suffer severe complications **(3, 4)**.

In pregnancy, COVID-19 is associated with an increased risk of maternal and neonatal morbidity, mortality, and respiratory infections, including severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and H1N1 influenza **(5, 6)**, even though reliable data are limited.

Therefore, we aimed to investigate the adverse effects of COVID-19 infection on maternal and neonatal outcomes in the pregnant population living in the east of Tehran, Iran.

Methods

This prospective cohort study was conducted at Arash Women's Hospital, an educational hospital

affiliated with the Tehran University of Medical Sciences (TUMS). The hospital serves the residents of Eastern Tehran, most of whom are middle to low socioeconomic status, as a referral and counseling center. The protocol of this study was approved by the Ethics Committee of the Deputy of Research Affairs, TUMS, Tehran province, Iran (IR.TUMS.MEDICINE.REC.1399.565). Participants in this study were enrolled between October 1, 2020, and August 1, 2021, and provided their informed consent voluntarily.

Participants in the study were all pregnant women admitted to Arash Women's Hospital for delivery or obstetric complications. At admission time, the infected group had a positive RT-PCR (reverse transcriptase polymerase chain reaction) test for COVID-19 performed on a nasopharyngeal swab sample, as well as at least three symptoms **(7)** or highly specific findings on a chest computed tomography (CT) scan for COVID-19 **(8)**. According to hospital protocol, this group of patients was cared for in a separate ward. Those with a history of COVID-19 infection or contact with an infected person, attendance in crowded, indoor places, clinic or hospital attendance, or traveled within the last two weeks were excluded from the control group. All participants were followed until discharge after delivery, and their obstetric and neonatal outcomes were assessed.

A specialized labor nurse or a resident physician filled out a standardized questionnaire including data on demographic characteristics, obstetrics and gynecologic history, medical history, data on the current pregnancy and parturition, and neonatal data for all participants. Quantitative variables are described using mean ± SD or median (interquartile range). Categorical variables are summarized as frequency and percentage. The two groups of participants were compared using the t-test for continuous variables and $\chi 2$ or Fisher exact test for categorical variables. Logistic regression was performed to examine the relationship between COIVD-19 infection, preterm labor, hypertension, maternal age, and neonatal outcome. Statistical analyses were performed using SPSS version 21.0 (IBM Corp., Armonk, NY, USA). $P < 0.05$ was considered statistically significant.

Results

A total of 701 women were admitted to our hospital, and 587 of them were pregnant. Among the pregnant patients, 108 (33.9%) had COVID-19 infection. We matched 211 pregnant women as the control group. Finally, 319 pregnant women were eligible and evaluated for maternal and neonatal outcomes. The mean age of participants was 30.52 ± 5.982 (range: 26-35). Hypertension, gestational diabetes mellitus (GDM), and hypothyroidism, which were set as maternal comorbidities, were reported in 34 (10.7%), 45 (14.1%), and 50 (15.7%) participants, respectively. Other characteristics of our sample population regarding the COVID-19 infection status are summarized in Table 1.

Table 1. Baseline characteristics of the participants.

	Pregnant women with mild COVID-19 infection (n=108)	Healthy pregnant women (n=211)	P-Value
Age	31.75± 5.48	29.9 ± 6.14	0.009*
Nationality			
Iranian	97 (89.8)	164 (77.7)	0.009*
Afghan	11 (10.2)	47 (22.3)	
Educational level			
Illiterate	6 (5.7)	24 (11.4)	0.013*
Primary/ Middle school	25 (23.6)	69 (32.7)	
High school/ College degree	51 (48.1)	95 (45.0)	
Bachelor's degree and higher	24 (21.7)	23 (10.9)	
Comorbidities			
Hypertension	13(12)	21(10)	0.57
Gestational Diabetes Mellitus	16(14.8)	29(13.7)	0.86
Hypothyroidism	18(16.7)	32(15.2)	0.74
Preterm delivery risk factors			
Impaired fetal heart rate	30 (28)	31 (14.7)	0.006*
Rupture of the membranes> 18 hours	9 (8.4)	10 (4.7)	0.215

	Pregnant women with mild COVID-19 infection (n=108)	Healthy pregnant women (n=211)	P-Value
Maternal delivery outcome			
Discharged	96 (88.9)	202 (95.7)	0.03*
Hospitalized	12 (11.1)	9 (4.3)	
Gestational age at Delivery	36.77 (36-38)	37.8 (37-39)	<0.001*
Delivery type			
NVD	18 (16.7)	81 (38.6)	<0.001*
C/S	90 (83.3)	129 (61.4)	
Neonatal outcome			
1st hour skin contact	51 (47.2)	160 (75.8)	<0.001*
1st hour skin contact	36 (33.3)	135 (64)	<0.001*
Apgar score			
1st minute	8 (8-9)	9 (8-9)	0.008*
5th minute	9 (9-10)	10 (9-10)	0.007*
Obstetrics history			
Gravidity	2 (1-3)	2 (1-3)	0.078
Parity	1 (0-1)	1 (0-2)	0.019*
Miscarriage	0 (0-3)	0 (0-4)	0.86
Live children	1 (0-3)	1 (0-4)	0.022*
IUFD	1 (0.9)	6 (2.8)	0.43
IUGR	7 (6.5)	15 (7.1)	1

NVD: Natural vaginal delivery; C/S: Cesarean section; IUFD: Intrauterine Fetal Death;IUGR: Intrauterine Growth Restriction.
***Data are presented as mean ± standard deviation, median (interquartile range) or number (percentage).**

Preterm birth (PTB), defined as delivery before 37 weeks of gestation, is the primary outcome of our study and was indexed in 71 (22.3%) participants. As summarized in Table 2, mothers who had PTB had significantly older age (32.69, IQ: 28-38 vs 28.89, IQ: 28–38 years old, P=0.001). Mothers who underwent PTB were more infected with COVID-19 than women who gave birth at term (47.9% vs 30%, p value=0.007). We entered significant factors in a binary logistic regression as covariates to predict the incidence of preterm delivery. As shown in Table 3, maternal hypertension was the most decisive risk factor with a relative risk (RR) of 5.40 (CI of 95%: 2.46-11.82, p≤0.001). Interestingly, mothers with a mild COVID-19 infection had a RR of 2.05 (CI of 95%: 1.15-3.64, p=0.014) compared to ones who were naïve to this infection during their pregnancy. Moreover, neonates from older mothers will suffer from PTB at an increased risk (RR=1.054, CI of 95%:1.001-1.109, p=0.044).

Table 2. Characteristics of participants with preterm labor

	GA at delivery < 37 (n=71)	GA at delivery ≥ 37(n=247)	P-Value
Age	32.69 ± 5.80	28.89 ± 5.91	0.001*
Nationality			
Iranian	62 (87.3)	198(80.2)	0.22
Afghan	9 (12.7)	49(19.8)	
Educational level			
Illiterate	5(7.1)	25(10.2)	0.30
Primary/ Middle school	18(25.7)	76(30.9)	
High school/ College degree	32(45.7)	113(45.9)	
Bachelor's degree and higher	15(21.4)	32(13)	

	GA at delivery < 37 (n=71)	GA at delivery ≥ 37(n=247)	P-Value
Comorbidities			
Hypertension	20(28.2)	14(5.7)	≤0.001*
Gestational Diabetes Mellitus	16(22.5)	29(11.7)	0.032*
Hypothyroidism	13(18.3)	37(15)	0.57
Gravidity	2.45 (1-3)	2.36 (1-3)	0.968
Parity	0.87 (0-1)	1.01 (0-2)	0.15
COVID-19 Infection	34 (47.9)	74 (30)	0.007*

GA: Gestational Age.
Data are presented as mean ± standard deviation, median (interquartile range) or number (percentage).

Table 3. Logistic Regression for prediction of preterm labor in participants

	B	RR (95% CI)	P-Value
Age	0.052	1.054 (1.001-1.109)	0.044*
Hypertension	1.687	5.40 (2.46-11.82)	≤0.001*
COVID-19 Infection	0.719	2.05 (1.15-3.64)	0.014*

RR= Relative risk, B= regression coefficient, CI= Confidence Interval

As shown in Table 4, the neonatal outcome as the secondary outcome of this study was divided into hospitalization or discharge after delivery and evaluated across maternal characteristics. The exact fisher's test demonstrated that neonates of Iranian mothers were hospitalized more often than those of Afghan mothers (51.34% vs 36.2%, p=0.042). Same as PTB, mothers with older age were more prone to deliver neonates who needed additional hospital management than younger mothers (31.46, IQ=27-36 vs 29.64 IQ=25-34 years old, p=0.009). Maternal GDM and hypothyroidism didn't differ significantly across neonatal hospitalization, but maternal hypertension was more significantly reported in mothers of hospitalized neonates (17.4% vs 4.3%, p≤0.001). Moreover, COVID-19 infection was reported significantly more prevalent in mothers whose neonates needed hospital admission (45.8% vs 22.6%, ≤0.001). In the last step, a multivariate binary logistic regression using the forward LR method was invoked to evaluate the independent association of the above-mentioned significant factors with neonatal outcome. After PTB, with a RR of 5.936 (CI of 95%:2.954-11.927, p≤0.001), maternal hypertension was the strongest predictor of the neonatal need for hospitalization with a RR of 2.737 (CI of 95%:1.066-7.025, p=0.036). Regarding maternal COVID-19 infection during pregnancy, it could predict the risk for neonatal hospitalization even more significant than the risk of PTB (RR=2.57, CI of 95%:1.532-4.318, p≤0.001).

Table 4. Maternal characteristics across the neonatal outcome

	Neonatal outcome		P-Value
	Discharged (n=164)	Hospitalized(n=155)	
Age	29.64 ± 5.92	31.46 ± 5.92	0.006*
Nationality			
Iranian	127(77.4)	134(86.5)	0.042*
Afghan	37(22.6)	21 (13.5)	
Education			
Illiterate	18(11)	12(7.8)	0.639
Primary or Middle school	51(31.1)	43(28.1)	
High school diploma/ college degree	73(44.5)	73 (47.7)	
Bachelor degree or higher	22(13.4)	25 (16.3)	
Comorbidities			

	Neonatal outcome		P-Value
	Discharged (n=164)	Hospitalized(n=155)	
Hypertension	7(4.3)	27(17.4)	≤0.001*
Gestational Diabetes Mellitus	17(10.4)	28(18.1)	0.054
Hypothyroidism	28(17.1)	22(14.2)	0.53
COVID-19 Infection	37 (22.6)	71(45.8)	≤0.001*

Data are presented as mean ± standard deviation or number (percentage).

Discussion

COVID-19 infection during pregnancy may increase the risk of preterm birth (PTB), cesarean section (C/S), and neonatal hospitalization. A number of studies have reported that pregnant women with COVID-19 have a higher rate of PTB than those with the general obstetric population **(9)**. PTB is not yet known to be caused directly by COVID-19 or if there are other cofactors that worsen maternal and fetal conditions. An analysis of 100 pregnant women infected with COVID-19 found a significant association with PTB, especially among those with fever **(10)**. There has been a correlation between PTB and body mass index (BMI) in mothers with COVID-19 symptoms **(11, 12)**, according to two studies. The results of our study showed that hypertension was associated with PTB in mothers with mild COVID-19 infection. As compared with asymptomatic mothers, symptomatic COVID-19 increased the risk of PTB and C/S **(12)**. Comparatively, a retrospective case-control study found that PTB rates were lower in 86 pregnant women with COVID-19 than before the pandemic **(13)**. Mothers with COVID-19 infection may experience a higher rate of PTB spontaneously or due to premature rupture of membranes (PROM). A recent Dutch study showed that measures to reduce COVID-19 infections during pregnancy led to a lower incidence of PTB **(14)**.

A significant difference in C/S rate was observed between infected and non-infected mothers in our study (83.3% versus 61.4%), whereas the overall C/S rate in our hospital at the time was 64.4%. These findings are similar to what has been reported in previous studies **(12, 15, 16)**. A review of 36 articles indicated that pregnant women with COVID-19 infection had a higher rate of C/S (68.9%) than other women. The presence of maternal COVID-19 was the only indication for a C/S in some cases **(17)**.

We found that newborns of mothers infected with COVID-19 were 2.57 times more likely to be hospitalized. According to different studies, 2 to 30% of neonates whose mothers had COVID-19 infection were admitted to the Neonatal Intensive Care Unit (NICU) **(13, 18)**. Our study suggests that maternal COVID-19 infection during pregnancy, PTB, and hypertension may increase the risk of neonates' admission to the NICU. Our findings are similar to those of Singh et al. **(18)**, who showed an increase in neonatal hospitalizations in NICUs. A Turkish study found that 6.4% of newborns whose mothers had COVID-19 infection were admitted to the NICU. In addition, C/S, PTB, and low birth weight were observed in 71.2%, 26.4%, and 12.8% of pregnancies, respectively **(19)**.

Following delivery, mother and newborn skin-to-skin contact increases the proportion of exclusively breastfeeding, both during the hospital stay and for a long time thereafter **(20)**. In an analysis of COVID-19 maternal and newborn care guidelines from 33 countries, only 21% recommended breastfeeding one hour after birth for neonates whose mothers were infected with COVID-19 **(21)**. The decision to allow skin-to-skin contact was made jointly by mothers and healthcare teams after assessing the risks and benefits, as no clear evidence supports an increased risk of COVID-19 transmission **(22, 23)**.

Conclusion

In our study, skin-to-skin contact and breastfeeding in the first hour were significantly lower in COVID-19 cases than in controls. At the time of this study, pregnant mothers in Iran were not recommended to receive the COVID-19 vaccine. Consequently, the effect of this disease on a pregnant woman without artificial immunity has been studied, which is strength of this study. Future studies should evaluate the effects of COVID-19 infection on pregnancy outcomes based on the number of doses and types of vaccines used. The prevalence of PTB, C/S, and neonatal hospitalization seems to be higher among mothers with mild COVID-19 infections than among healthy mothers.

Acknowledgments

The authors would like to express their appreciation to all the individuals who participated in this study.

Authors' Contribution

Each author participated in data analysis, drafting, and revising of the manuscript, and consented to assume responsibility for all aspects of this project.

Conflict of Interest

The authors declared no conflicts of interest.

Funding

The research was not specifically funded by any public, commercial, or not-for-profit agencies.

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How to Cite This Article:

Aghajani, F., Nariman, S., Alirezaei, M., Maleki, Z., Moghbel Baerz, M., Pakbaz, et al. Comparison of Obstetric and Neonatal Outcomes in Pregnant Women with and Without COVID-19 Infection: A Single-Center Prospective Cohort Study. J Obstet Gynecol Cancer Res. 2024;9(5):542-8.

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