

## RESEARCH ARTICLE

# Comparison of Maternal and Neonatal Outcomes Among COVID-19 and Healthy Pregnant Women in the West of Iran: A Retrospective Cohort Study

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**Abstract: Background:** In the COVID-19 epidemic, pregnant women, fetuses, and newborns are a high-risk population that is more susceptible than the general population. These groups are more susceptible to serious respiratory illnesses and pneumonia because of their weakened immune systems. This study compared maternal and neonatal outcomes in postpartum women with COVID-19 with similar healthy women at the hospital.

**Methods:** In this retrospective cohort study, the characteristics of 100 pregnant women with COVID-19 (confirmed by a positive PCR test during pregnancy) were compared to 150 healthy pregnant women who were referred to Fatemeh Hospital in Hamadan from March, 2020 to February, 2021. The maternal and neonatal outcomes were collected from the medical record of patients and analyzed using SPSS software (Ver. 26).

**Results:** No significant differences were observed in the average ages ( $\pm$  standard deviation) of the two groups of COVID-19 ( $30.25 \pm 6.24$  years) and healthy ( $29.48 \pm 6.73$  years) women. In this study, pregnant women were infected with COVID-19 from weeks 7 to 41 of gestation, with a median infection time of 35 weeks. The odds ratio (95% confidence interval) of pre-eclampsia and preterm birth was significantly higher in women with COVID-19 than in healthy women with the following values 2.79 (1.61, 7.34) and 22.26 (2.86, 173.33), respectively.

**Conclusion:** Pregnant women suffering from COVID-19 had considerably greater rates of gestational issues, neonatal difficulties, pre-eclampsia, and premature delivery, according to the findings of this study. During epidemics, it is advised that pregnant women and their newborns receive more basic care.

**Keywords:** COVID-19, pregnant women, pregnancy outcome, neonatal, maternal-child health centers, PCR.

## 1. INTRODUCTION

In 2019, the coronavirus disease (COVID-19) was recognized as one of the severe human pathogens, the third outbreak of coronaviruses globally, and as an acute respiratory syndrome, which the later WHO introduced as a pandemic [1-3]. According to the statistics announced by this organization, until February 23<sup>rd</sup>, 2021, 111,419,939 people

have been infected worldwide, and about 4,357,427 have died. At the same time, there have been 1,582,275 verified cases of Covid-19 in Iran, with 57,259 deaths [1, 4]. Many studies have investigated clinical manifestations, transmission, prevention, and treatment of this disease [3, 5, 6]. According to the CDC report, the most common symptoms of COVID-19 in the general population included cough (84%), fever (80%), myalgia (63%), fatigue (62%), headache (59%), and shortness of breath (57%). Less common symptoms were sputum production, muscle pain, and a few gastrointestinal symptoms, such as diarrhea [7]. This disease is considered a serious emergency for public health, especially

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in vulnerable populations, such as pregnant mothers [8]. It is natural that with the increase in the coronavirus outbreak, the infection in pregnant mothers is also increasing [9]. Pregnancy is one of the most significant periods of life, and pregnant women experience different physical and mental changes during this period [10, 11]. The natural physiological changes in pregnant mothers, including changes in the immune system and lung function, lead to an increase in their sensitivity and vulnerability to diseases [7]. On the other hand, as the pregnancy progresses and the fetus grows, the uterus occupies more space, and with the upward movement of the diaphragm and the decrease in breathing capacity, the mother is exposed to lung infection [12]. Along with these changes, the COVID-19 virus can create worse conditions for the mother and baby.

Many studies have investigated maternal and neonatal outcomes in mothers with COVID-19. The results showed that cesarean delivery, low birth weight, premature labor, and premature birth are the most likely complications of pregnancy outcomes [3, 13]. Premature birth, abortion, intrauterine growth restriction, hospitalization of newborns in the intensive care unit, and fetal distress are known as the most likely neonatal complications [4, 11, 12, 14-16].

Some studies have reported the effect of COVID-19 on placental inflammation and pregnancy complications, such as pre-eclampsia [17, 18]. On the other hand, some studies showed that the possibility of complications, such as pre-eclampsia in mothers with COVID-19, is not different from non-infected pregnant mothers [19]. Therefore, there is a need to investigate the effect of COVID-19 on pre-eclampsia.

A case-control study in Hamadan in 2019 compared pregnancy outcomes between asymptomatic and symptomatic pregnant women with COVID-19. The results showed that cesarean delivery and low birth weight in pregnant women with symptoms were significantly more than in women without symptoms [4, 15].

Considering that variables, such as pre-eclampsia, type of delivery, IUFD, birth weight, fetal distress, and preterm birth, can affect the health of the mother and fetus and the studies that have been conducted in the world have examined the impact of COVID-19 on these maternal and newborn outcomes, we decided to compare these variables in infected and non-infected pregnant mothers. Since few studies have been conducted in Iran on the comparison of pregnancy outcomes in two groups of pregnant women with and without COVID-19 [4, 5, 9, 15], it is not possible to give a definite opinion on this matter, and there is a need for more studies. Moreover, the epidemic of the COVID-19 virus, the importance of women's health, and the concerns in this field, led to the investigation and comparison of pregnancy and newborn outcomes in pregnant women infected and not infected with COVID-19 in the west of Iran.

## 2. MATERIALS AND METHODS

In this retrospective cohort study, the participants were 250 pregnant women who consisted of 100 COVID-19 and 150 healthy women with homogeneous maternal and gestational age referred to Fatemeh Hospital in Hamadan, west-

ern Iran, for delivery from March, 2020 to February, 2021. The COVID-19 group consisted of women whose definitive diagnosis of COVID-19 was confirmed by polymerase chain reaction (PCR) and who were hospitalized during pregnancy. The sample was collected by nasopharyngeal swabs of the upper respiratory tract to confirm COVID-19. These women were followed up until delivery, and their maternal and neonatal outcomes were evaluated at the delivery time. The individuals in the healthy group were selected from healthy pregnant women who were referred to this center for delivery on the first to the third day of each month during study time. This study was approved by the Hamadan University of Medical Sciences (IR.UMSHA.REC.1399.1023). Inclusion criteria for the COVID-19 group were confirmed by PCR test and the absence of a specific underlying disease (e.g., respiratory disease, hypertension). For pregnant women in the healthy group, the inclusion criteria were the absence of a specific underlying disease (e.g., respiratory disease, hypertension). Exclusion criteria in both groups consisted of multi-fetal pregnancy.

To estimate sample size, the formula and prevalence of low birth weight in symptomatic and asymptomatic pregnant women with COVID-19 were considered (0.267 vs. 0.088, respectively) [4], with a significant level of  $\alpha = 0.05$  and power of  $1 - \beta = 0.90$ . A sample size of 96 pregnant women for each group was calculated. To increase the precision, we selected the number of healthy pregnant women 1.5 times the number of pregnant women with COVID-19. According to the inclusion criteria (absence of a specific underlying disease) in this study, 110 pregnant women with COVID-19 were included in the exposure group. Among 110 eligible participants, eight were lost during the follow-up period, and two were excluded for other reasons. Thus, the number of subjects who remained for data analysis comprised 250 participants.

The data were collected from patients' medical records which was registered at the time of delivery by a trained nurse using a predetermined checklist containing demographic characteristics, such as age (year), educational level (under diploma, diploma, and university), residency (village, city), blood group (A, B, AB, and O), Rhesus (Rh) factor (positive, negative), Laboratory findings, such as the counts of white blood cells (WBC,  $\mu\text{L}$ ), hemoglobin (Hb, g/dl) and platelets count ( $\mu\text{L}$ ), clinical symptoms for the COVID-19 group, such as fever, cough, dyspnea, muscle spasms, gastrointestinal symptoms, and other symptoms, pregnancy outcomes, such as gestational diabetes (yes, no), postpartum (normal vaginal delivery (NVD), caesarean section (SC)), urgency in delivery (emergency, elective), pre-eclampsia, neonatal outcomes, such as gestational age (week), birth weight (g), birth height (cm), 1- and 5-minute Apgar scores, newborn head circumference (cm), intrauterine fetal death (IUFD), neonatal death (yes, no), preterm birth (yes, no), meconium (yes, no), fetal distress (yes, no), decreased movement (yes, no), and premature rupture of membranes (PROM). The Helsinki Declaration was followed for involving human subjects in the study, and informed consent was obtained from all pregnant women during delivery time. Descriptive statistics were reported, such as mean  $\pm$  SD, frequency, and percentage. Continuous characteristics between two groups were compared using Mann-

Whitney or t-test, and qualitative characteristics were compared between two groups by Chi-square. The effect of COVID-19 infection was specifically assessed on each maternal and neonatal outcome, including 20 outcomes, separately by univariate logistic regression and reported with Unadjusted Odds Ratios (UORs). To prevent increasing type 1 error rate, Holm correction was utilized for adjusting the p-levels. Due to a large number of outcomes, running regression models by adjusting other covariates for all outcomes was not rational. Therefore, multiple regression models were performed for outcomes with significant UOR effects of COVID-19, considering education and residence. All analyses were applied in SPSS version 26 software, and P-value less than 0.05 was considered the significant level.

### 3. RESULTS

In this retrospective cohort study, the participants were 250 pregnant women who consisted of 100 COVID-19 and 150 healthy women referred to the hospital for delivery. The mean ages ( $\pm$  standard deviation) of COVID-19 and healthy groups were  $30.25 \pm 3.24$  and  $29.48 \pm 6.73$ , respectively ( $p=0.363$ ). Pregnant women with COVID-19 were infected between 7 and 41 weeks of pregnancy, with a median infection time of 35 weeks. The prevalence rates of clinical symptoms in the patients were in the descending order of fever (58, 58%), cough (53, 53%), dyspnea (22, 22%), muscle spasms (20, 20%), and gastrointestinal symptoms (12, 12%). Other symptoms (*e.g.*, loss of smell and taste senses, headache, rhinorrhea, sore throat, chills, and itching) were observed in nine (9%) patients. The results in Table 1 show that the distributions of education and residence were signif-

icantly different in the two COVID-19 and healthy groups. The percentage of under-diploma education and residence in a village in the COVID-19 group was significantly lower than the healthy group (for education: 70% vs. 82%; for residence: 39% vs. 55.3%, respectively). However, no significant relationships were found between the urgency in delivery and the infection of pregnant women. Blood groups and RH had almost the same distribution in both groups.

Table 2 compares the laboratory outcomes in two healthy and COVID-19 groups. Moreover, white blood cell (WBC) count ( $8703.30 \pm 3777.96$  vs.  $10706 \pm 2957.4$ ) and hemoglobin ( $12.32 \pm 1.47$  vs.  $13.07 \pm 1.24$ ) were significantly lower in COVID-19 patients ( $P=0.001$ ), but two groups were not significantly different in the platelet count ( $192.66 \pm 66.52$  vs.  $204.77 \pm 73.99$ ).

As shown in Table 3, comparing neonatal outcomes in healthy and COVID-19 groups presented that the mean values of 1- and 5-minute Apgar scores, as well as newborn's height, in COVID-19 women were considerably lower than those of healthy individuals. There were no statistically significant differences among the birth weight and head circumstances of these two groups.

Based on our findings, pregnant women with COVID-19 were significantly at higher risk of pre-eclampsia and preterm birth compared to healthy women. The unadjusted OR estimates of pre-eclampsia and preterm birth in women with COVID-19 were 2.79 (95% CI: 1.6, 7.34) and 22.26 (2.86, 173.33), respectively. There was no significant association between COVID-19 and other neonatal and maternal outcomes (Table 4).

**Table 1. Baseline characteristics in both COVID-19 and healthy pregnant women.**

-		COVID-19 Number (percent)	Healthy Number (percent)	P-value
Education	Under diploma education	70 (70)	123 (82)	0.027
	Diploma and university	30 (30)	27 (18)	
Residence	City	61 (61)	67 (44.7)	0.011
	Villages	39 (39)	83 (55.3)	
Postpartum	NVD	48 (48)	75 (50)	0.757
	C/S	52 (52)	75 (50)	
Urgency in Delivery	Emergency	26 (26)	35 (23.3)	0.631
	Elective	74 (74)	115 (76.7)	
Blood Group	A	31 (35)	49 (32.7)	0.852
	B	21 (23.6)	34 (22.7)	
	AB	5 (5.6)	13 (8.7)	
	O	32 (36)	54 (36)	
RH	+ve	73 (82)	135 (90)	0.076
	-ve	16 (18)	15 (10)	

Table 2. Comparison of neonatal outcomes in two groups.

Laboratory Findings	Normal Range <sup>a</sup>	Covid-19 Mean (SD)	Healthy Mean (SD)	P-value
WBC (×1000μL)	5.6-16.9	8703.3 (3777.9)	10706 (2957.4)	0.001
Hb (g/dl)	9.5-15.0	12.31 (1.47)	13.07 (1.24)	0.001
Plateletes (×1000μL)	146-429	192.7 (66.5)	204.7 (73.9)	0.188

Note: a: A bbassi- Ghanavati [24]

Abbreviation: SD: Standard Deviation.

Table 3. Comparison of neonatal outcomes in two groups.

-	COVID-19 Mean (SD)	Healthy Mean (SD)	P-value
Apgar score (first minute)	8.57 (1.12)	8.83 (0.56)	0.031
Apgar score (fifth minute)	9.65 (.84)	9.85 (.47)	0.031
Birth weight(gr)	3031.76 (629.76)	3048.41 (580.43)	0.832
Newborn's head circumference (cm)	34.88 (2.82)	34.79 (1.71)	0.799
Newborn's height (cm)	49.67 (3.79)	50.81 (3.11)	0.021

Abbreviation: SD: Standard Deviation.

Table 4. Association of COVID-19 disease with neonatal and maternal outcomes using an unadjusted logistic model.

Outcome	COVID-19 Number (Percent)	Healthy Number (Percent)	OR (CI 95%)	P-value
<b>Maternal outcomes</b>	-			
Diabetes	4.00 (4%)	0 (0.00)	-	-
Postpartum	53.00 (53%)	75 (50)	1.13 (0.68, 1.87)	0.642
Urgency in delivery (Emergency)	27.00 (27%)	35 (23.33)	1.22 (0.68, 2.2)	0.511
Pre-eclampsia	12.00 (12%)	7 (4.67)	2.79 (1.6, 7.34)	0.038
PROM	7.00 (7%)	0 (0.00)	-	-
<b>Neonatal outcomes</b>	-			
Low birth weight	20.00 (20%)	24 (16)	1.31 (.68, 2.53)	0.417
IUFD	3.00 (3%)	0 (0.00)	(0.00, 0.00)	-
Neonatal death	2.00 (2%)	1 (0.67)	3.04 (.27, 34.00)	0.367
Preterm birth	13.00 (13%)	1 (0.67)	22.26 (2.86, 173.33)	0.003
Meconium	3.00 (3%)	6 (4)	0.74 (0.18, 3.04)	0.679
Fetal distress	2.00 (2%)	2 (1.33)	1.51 (0.21, 10.99)	0.683
Decreased movement	1.00 (1%)	7 (16)	0.21	0.143

As shown in Table 1, the distributions of education and residence were significantly different in the two COVID-19 and healthy groups. To ascertain the confounding effect of education and residence variables on preterm birth, pre-eclampsia, Apgar score (first and fifth minute), and newborn's height, multiple logistic regression models were uti-

lized. As observed in Table 5, these two variables do not have any significant effect on the outcomes.

#### 4. DISCUSSION

The maternal and neonatal outcomes of COVID-19 postpartum women were compared to those of similar

Table 5. Association of COVID-19 disease with neonatal and maternal outcomes using an adjusted regression model.

Preterm				
Covariate	Estimate	SE	P-Value	OR (95% CI)
Status (COVID)	3.16	1.05	0.003	23.47 (2.98, 187.68)
Residence (City)	0.01	0.59	0.989	1.01 (0.32, 3.22)
Education (Under Diploma)	0.47	0.70	0.507	1.59 (0.40, 6.35)
Pre-Eclampsia				
Status (COVID)	1.001	.505	.048	2.72 (1.01, 7.33)
Residence (City)	-.529	.520	.309	0.59 (0.21, 1.63)
Education (Under Diploma)	-.779	.545	.153	0.46 (0.16, 1.34)
Apgar1				
Status (COVID)	.263	.110	.017	-
Residence (City)	.049	.112	.663	-
Education (Under Diploma)	.042	.133	.750	-
Apgar5				
Status (COVID)	.201	.085	.019	-
Residence (City)	.028	.087	.747	-
Education (Under Diploma)	.013	.104	.900	-
Newborn's Height				
Status (COVID)	1.104	.499	.028	-
Residence (City)	.195	.528	.712	-
Education (Under Diploma)	-.138	.609	.822	-

healthy women in this study. The main results of this study were that the odds ratio of pre-eclampsia and preterm birth was significantly higher in women with COVID-19 than in healthy women.

As expected, a significant association was observed between educational and residence levels in the two groups. The significant proportion of rural women with a high school education implies that this community has a low level of knowledge, culture, and lack of access to information or specialized training on COVID-19 care. The significantly high numbers of urban residents compared to the rural population revealed relatively easier accessibility of the former, the high population, higher traffic rates of the urban population, and its inevitable consequences, which are less frequent in rural areas.

In this research, the results showed that pregnant women with COVID-19 had a higher rate of preterm delivery than healthy women. In line with this research, London *et al.* reported greater rates of preterm delivery in pregnant women with COVID-19 than in other pregnant mothers ( $P$ -value = 0.007) [20].

According to our findings, the means of 1- and 5-minute Apgar scores and Newborn's height were significantly lower in postpartum women with COVID-19 than in healthy ones. In comparison, the head circumference and birth weight were not significantly different in the two groups, possibly caused by preterm delivery in terms of COVID-19 infection. However, in a similar study, Jenabi *et al.* found a significant difference. Moreover, they reported a lower birth weight in symptomatic women with COVID-19 than that in asymptomatic pregnant women. In a descriptive longitudinal study on 133 pregnant women, Azh *et al.* detected maternal outcomes, including premature rupture of membranes (3.2%), cesarean section (1.51%), maternal mortality (5 cases, 28.11%), neonatal outcomes of neonatal death (3%), and prematurity (9%) in 96.87% of mothers infected with COVID-19 in the second and third trimesters of pregnancy. Our observations indicate higher preterm delivery in pregnant women with COVID-19. Thus, the role of health protocol education and the need for prenatal care should be highlighted to reduce maternal and neonatal complications. In a study, the O<sup>+</sup> blood group was reported to be a significant factor in women [21]. In a review study, Nikpour *et al.* evaluated the clinical manifestations and maternal outcomes

in pregnant women with COVID-19. They found that preterm delivery and cesarean section rate were more common in these women. The most frequent laboratory results were decreased blood lymphocytes and increased CRP, corresponding to the present findings [9].

In a descriptive case study conducted by Moaya *et al.*, all pregnant women referred for delivery and presented with suspicious symptoms of COVID-19 were evaluated for maternal and neonatal complications. Fever was the most prevalent symptom of the disease [20]. The present study similarly reported fever and dyspnea in more than half of pregnant women. None of the pregnant women needed assisted breathing apparatus. High CRP and pulmonary involvement were observed on lung CT scans of all patients. Five infants were naturally born, one preterm infant and one infant weighing < 2500 g and two infants with COVID-19 symptoms were hospitalized after birth, although PCR tests were negative for both [22].

The symptoms of fever and dyspnea in more than half of pregnant women indicated the need to reinforce the immune system and provide more care for pregnant women during epidemics. Decreased hemoglobin levels and WBC count in the COVID-19 group were the other findings of this study, which partially confirmed those of Chen *et al.* and Sasson *et al.* [12, 23]. The platelet count, on the other hand, was normal in both groups, with no significant differences. The usual distribution of blood groups in pregnant women with COVID-19 showed that all blood groups are virtually equally susceptible to the condition. Although some reports suggested that blood group A was susceptible to COVID-19, recent reports indicated a similar distribution of all blood groups in people being affected with this disease. The significant association between COVID-19 and pre-eclampsia in pregnant women in our study probably results from blood reactions and its increasing effect on gestational hypertension, which requires further and more careful examination of pregnant women in epidemics. Two (2%) deaths of infants, whose mothers presented severe symptoms at the admission time and whose lungs were completely involved, is an alarm for the need for better and more education and care of women during pregnancy and delivery, particularly at the time of epidemics.

For pregnant women, societal preventative measures are required. Prenatal care and adherence to health guidelines in pregnant women should also be overseen by health centers under special monitoring. The global evidence regarding the virus needs significant research and the elimination of confounding variables. However, there were some limitations to this study. As the sample size was limited, all potential confounders could not be controlled. It is recommended that future studies use a larger sample size. Another limitation was that there could be selection bias in the hospital while selecting COVID-19 patients. Another was the lack of follow-up of mothers and infants during the postpartum period. Thus, it is recommended to investigate the maternal and neonatal results in the postpartum period. Moreover, there were differences in education and residence, possibly confounding our results. We performed a sensitivity analysis and showed that the results were the same after running regression models.

## CONCLUSION

According to the findings of the present study and previous studies in recent years, pregnant women are potentially at more risk of infectious diseases and epidemics. Therefore, the expansion of maternal/neonatal care is recommended during and after pregnancy, along with further studies.

## LIST OF ABBREVIATIONS

IUFD	=	Intrauterine Fetal Death
NVD	=	Normal Vaginal Delivery
PCR	=	Polymerase Chain Reaction
PROM	=	Premature Rupture of Membranes
SC	=	Cesarean Section

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the ethics committee of Hamadan University of Medical Sciences, Iran (Ethics code IR.UMSHA.REC).

## HUMAN AND ANIMAL RIGHTS

No animals were used in the studies that are the basis of this research. All the humans procedures were followed in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2013 (<http://ethics.iit.edu/ecodes/node/3931>).

## CONSENT FOR PUBLICATION

Informed consent was obtained from all pregnant women at delivery time.

## STANDARD OF REPORTING

STROBE guidelines were followed.

## AVAILABILITY OF DATA AND MATERIALS

The authors confirm that the data supporting the findings of this research are available within the article.

## FUNDING

None.

## CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

## ACKNOWLEDGEMENTS

The authors would like to appreciate the sincere support of the vice-chancellor for Hamadan University of Medical Sciences, Fatemieh Clinical Research Development Unit, Hamadan, and the respected staff of the prenatal ward.

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