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Maternal, Fetal and Neonatal Outcomes in Hospitalized Pregnant Women with Covid-19 in Northern Iran: A Prospective Study

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ABSTRACT

Background & Objective: The Covid-19 pandemic can cause complications for pregnant women and more serious maternal, fetal and neonatal care related to this disease should be considered in health systems. The aim of the present study was to investigate the maternal, fetal, and neonatal outcomes of pregnant women with COVID-19 disease.

Materials & Methods: We performed a prospective study with a longitudinal design of all pregnant women hospitalized due to moderate and severe COVID-19 referred to Al-Zahra hospital, Rasht, Iran. After patient discharge, patients were followed until delivery, maternal, fetal, and neonatal outcomes were assessed by a 4-part researcher-made questionnaire.

Results: In total, 166 pregnant women with Covid-19 were included in the study. The median gestational age in patients was 35.5 weeks and the median delivery age was 38 weeks. Delivery in 137 (82.5%) women were cesarean section and 29 (17.5%) had a vaginal delivery. The most common clinical symptoms among patients were fever, cough, and dyspnea with 50.9%, 38.5%, and 31.5% frequency, respectively, 9.6% had poor prenatal outcomes, 15 patients (9%) were admitted to ICU and 4 patients died (2.4%). Poor maternal outcomes were reported in 61.5% of patients with severe clinical symptoms, ($p < 0.001$). There was no significant relationship between the severity of the disease and the type of delivery ($p = 0.41$).

Conclusion: In our study we observed an increase in poor maternal, fetal and neonatal outcomes particularly in pregnant women with severe symptoms, although careful care is still recommended for affected pregnant women to reduce fetal, neonatal, and maternal complications. Further research will be needed to devise plan for pregnancy care and future health care crises.

Keywords: Covid-19, Pandemics, Pregnancy outcome, Infant

Introduction

Respiratory infection caused by SARS-CoV-2 (COVID-19 disease) is a deadly and spreading disease. In the last two decades, infections caused by other coronaviruses such as acute respiratory syndrome (SARS) and the Middle East acute respiratory syndrome (MERS) caused fatal respiratory diseases. The third virus in this family is SARS-CoV-2 which causes severe respiratory disease or COVID-19 **(1)**. Since its inception, disease control and prevention in pregnant women has become an important concern because little information is available on maternal, fetal, and neonatal complications **(1, 2)**. Pregnancy creates physiological conditions that predispose a person to viral diseases **(3)**. Due to the suppression of the immune system in pregnancy and the physiological changes of the respiratory system, pregnant women are prone to more respiratory injuries and severe pneumonia, which has been confirmed in influenza **(4)** and SARS **(5)**.

Preliminary reports in China of 18 pregnant women with COVID-19, all in their third trimester, showed that the clinical findings are similar to those in the general population, and there was no evidence that pregnancy increases the risk of COVID-19 **(1, 3, 6)**. The study showed that the clinical symptoms of pregnant women were similar to those of non-pregnant women. The most common symptoms in pregnant women were fever (rarely severe and above 39 °C) and cough, leukopenia, and increased alanine transaminase (ALT) and aspartate transaminase (AST). Fetal distress and preterm delivery have been reported in some cases, and almost all (except two) had a cesarean delivery, and the SARS-CoV-2 virus test result was negative in all neonates **(3,6)**. Studies have also shown that if the mother is infected in the third trimester, maternal-fetal vertical transmission does not occur **(6)**, the same was true for SARS **(5)**.

Since the disease can cause complications for pregnant women, more serious maternal and fetal care related to this disease should be considered in health systems **(1)**. Based on studies on the consequences of Covid-19 in pregnancy, it is still not possible to conclude with certainty about its complications **(7)** and in order to appropriate clinical management, there is still a need for more studies in this regard **(8)**. Also, the attention of health systems to provide care for Covid-19 patients and as a result, the reduction of prenatal care has led to the inadequacy of the health system to provide services to pregnant women, which could be one of the causes of maternal death during Covid-19 pandemic **(9, 10)**. Considering the high prevalence of COVID-19 in Iran, the present study was conducted to investigate the maternal, fetal, and neonatal outcomes of pregnant women with COVID-19 disease.

Methods

The present study was a prospective study with a longitudinal design. The study population was all pregnant women (confirmed by ultrasonography) with any gestational age with COVID-19 (using polymerase chain reaction (PCR) of throat and nose swab sample, which was confirmed by the infectious disease specialist) and were hospitalized due to moderate and severe COVID-19. They were referred to Al-Zahra hospital, Rasht, Iran, and examined by the census method from March 2020 to April 2021. A total of 166 pregnant women were studied. After patient discharge, patients were followed until delivery, and then maternal, fetal, and neonatal outcomes were assessed by a 4-part researcher-made questionnaire.

The first part included demographic information (age, education, and occupation of patient), obstetrics characteristics (gestational age, number of pregnancies, number of deliveries, history of abortion, history of intrauterine death, history of infertility, pregnancy after infertility treatment), and clinical and paraclinical symptoms of the patients were recorded at the time of diagnosis. In the second part of the questionnaire, maternal outcomes until delivery including admission to an intensive care unit (ICU), need for mechanical ventilation, renal failure, disseminated intravascular coagulation (DIC), sepsis, and maternal mortality were examined, and concomitant and underlying maternal diseases such as diabetes, hypertension and liver disease were recorded. Type of delivery and cause of cesarean section were also recorded. In the third part, poor prenatal outcomes including fetal abnormalities, spontaneous abortion, fetal death, and fetal growth restriction (FGR) were investigated. In the fourth part, postnatal information including sex, weight, height, and neonatal outcomes including preterm delivery, Apgar score, admission to neonatal intensive care unit (NICU), and neonatal death, were recorded.

Statistical analysis

The data were analyzed by the Statistical Package for the Social Sciences for Windows (SPSS, version 20, Company, Country) software. Quantitative data are presented as mean and standard deviation and median (Interquartile range) for description of normally and non-normally distributed data, respectively, and the qualitative data is displayed as number and percentage. The normality of the distributions was tested using the Kolmogorov-Smirnov test. To compare groups, the chi square test was used. The statistical significance of the tests was considered as $p < 0.05$.

Results

In total, 166 pregnant women with Covid-19 were included in the study. The mean age of the study participants was 31.6 ± 6.2 years. The median gestational age in patients was 35.5 weeks and the median delivery age was 38 weeks. The mean weight and height of neonates were 3178.5±638 grams, and 49±3.4 centimeters, respectively. 33.7% of people had a history of underlying disease. In terms of obstetrics-related variables, only one patient had a history of intrauterine fetal demise (IUFD). 9.1% of patients had a history of infertility. The most common clinical symptoms among patients were fever, cough, and dyspnea with 50.9%, 38.5%, and 31.5% frequency, respectively. Other symptoms are presented in the Table 1.

Table 1. Maternal demographics and symptoms in pregnancies with confirmed SARS-CoV-2 infection

Variables		All inclusions* (n=166)
Age (years)		31.6±6.2
BMI (kg/m2)		26.5(23.7-30.9)
Parity		2(1-3)
Gravidity		1(0-1)
Number of abortions		0(0-1)
Number of live birth		0(0-1)
Age of pregnancy (weeks)		35.5(28-38)
History of IUFD		1(0.6)
History of infertility		15(9.04)
History of underlying diseases		56(33.7)
Symptoms of Covid-19	Fever	82(50.9)
	Chills	42(62.1)
	Body pain	41(25.5)
	Tiredness	4(2.5)
	Nausea and vomiting	11(6.8)
	Sore throat	1(0.6)
	Dyspnea	51(31.5)
	Cough	62(38.5)
	Diarrhea	7(4.3)
	Headache	7(4.3)
	Chest pain	4(2.5)
	loss of smell	2(1.2)

***Data available for 166 women. Data are given as mean±SD, median (Interquartile range;%25-%75) or *n* (%).**
BMI: body mass index; IUFD: intrauterine fetal demise.

In this study, 16 patients (9.6%) had poor prenatal outcomes. Fifteen patients (9%) were admitted to the ICU. Five patients (3%) needed mechanical ventilation. Three patients (1.8%) had renal failure and DIC, two (1.2%) patients had sepsis, and finally, four (2.4%) patients died. The type of delivery in 137 (82.5%) women was cesarean section and 29 (17.5%) had a vaginal delivery. Other fetal and neonatal outcomes are presented in Table 2.

Table 2. Maternal, fetal and neonatal outcomes in pregnancies with confirmed SARS-CoV-2 infection

Outcomes		Frequency (%)
Severity of Covid-19	Moderate	140(84.3)
	Severe	26(15.7)
ICU admission		15(9)
Mechanical ventilation		5(3)
Renal failure		3(1.8)
DIC		3(1.8)
Sepsis		2(1.2)
Maternal mortality		4(2.4)
IUFD		6(3.6)

Outcomes		Frequency (%)
FGR		3(1.9)
Neonatal death		3(1.9)
Delivery time	Term	128(80)
	Pre-term	29(18.1)
	Post-term	3(1.9)
Type of delivery	Vaginal delivery	29(17.5)
	Cesarean section	137(82.5)
Reasons for cesarean section	Fetal distress	21(15.3)
	CPD	8(5.8)
	Repeated cesarean	59(43.1)
	Other	49(35.8)
Sex of neonate	Boy	76(47.8)
	Girl	83(52.2)
Admission to the NICU		26(16.25)
Apgar score at first minute below 7		12(16.9)
Apgar score at fifth minute below 7		4(5.6)

Data are given as *n* (%). †Number expressed as percentage of individual neonates/fetuses.
CPD: Cephalopelvic Disproportion; DIC: Disseminated intravascular coagulation

The results showed that the history of underlying disease in pregnant women with Covid-19 had no statistically significant relationship with the maternal and neonatal outcomes (Table 3). There was a statistically significant relationship between the severity of the Covid-19 disease and poor maternal outcomes. Poor maternal outcomes were reported in 61.5% of patients with severe clinical symptoms, and in 42.3% of patients, neonatal symptoms were reported (P <0.001). However, there was no significant relationship between the severity of the disease and the type of delivery (P = 0.41) (Table 4).

Table 3. Relationship between maternal underlying disease history and poor neonatal outcomes

		Maternal outcomes N=166		p-value*	Neonatal outcomes N=166		*P*-value*
		No	Yes		No	Yes	
History of underlying disease	No	100(90.9)	10(9.1)	0.73	7 5(68.2)	35(31.8)	0.96
	Yes	50(89.3)	6(10.7)		38(67.9)	18(32.1)	

. Chi-Square Test

Table 4. Relationship between Covid-19 disease severity and type of delivery and maternal and neonatal outcomes

		Type of delivery (N=166)		p-value*	Maternal outcomes N=166		p-value*	Neonatal outcomes N=166		p-value*
		Vaginal	Cesarean section		No	Yes		No	Yes	
Severity of	Moderate	23(16.4)	117(83.6)	0.41	140 (100)	0	0.0001	98(70)	42(30)	0.21

Covid-19	Severe	6 (23.1)	20(76.9)		10(38.5)	16(61.5)		15(57.7)	11(42.3)

*** Chi-Square Test**

Discussion

This longitudinal study investigated the poor fetal, maternal, and neonatal outcomes of Covid-19 in pregnant women. The mean age of patients in this study was 31.6 years, mostly in the third trimester of pregnancy, and most patients had no underlying disease.

Regarding the symptoms of the Covid-19 in infected pregnant women, in this study, most of the observed symptoms were mild and included fever, cough, and dyspnea, which were similar to non-pregnant women. This result is in line with the results of studies conducted in Iran **(11-14)** and other countries **(3, 15, 16)**. Also, the most common symptom of infected women in current studies was fever (50.9%), which is in line with the results of other studies in Iran (67.5%) **(12)**. Comparison of symptoms of pregnant women with non-pregnant women in studies showed that clinical symptoms in pregnant women with Covid-19 were not more advanced than non-pregnant women **(14, 15)**. Another study found that most pregnant women had mild symptoms **(16)**. This result was confirmed in the current study and severe symptoms were seen in 15.7% of cases and the rest of the patients had moderate symptoms. Poor maternal outcomes (ICU admission, DIC, etc.) were observed in 9.6% of patients.

The poorest outcome in pregnant women in the current study was the admission to the ICU (9%), which was no different from the non-pregnant population with Covid-19 in Iran **(17)**. This result was in line with the study of Vouga et al., that the rate of poor maternal outcomes was 9.9% **(18)**. Other severe complications such as the need for mechanical ventilation, renal failure, DIC, and sepsis were observed in a small number of patients. A similar study on severe complications of Covid-19 in 155 Iranian pregnant women showed that the admission of pregnant women to the ICU was 12.5%, which is higher than the present study **(13)**. In addition, in the present study, there was a statistically significant relationship between disease severity and poor maternal outcome (P <0.001), so that in 61.5% of pregnant women with severe clinical symptoms, the poor maternal outcome was reported. This result was in line with the study of Vouga et al. **(18)**. It is noteworthy that severe complications of Covid-19 are more common in pregnant women with underlying diseases **(18)**, so the absence of underlying disease in most women in the present study may explain the lower incidence of severe symptoms in pregnant women. Also, there was no significant association between underlying diseases and poor maternal outcomes (P = 0.738).

The maternal mortality rate in the current study was 2.4%. A similar study showed that severe cases of Covid-19 were associated with increased maternal and neonatal mortality **(19)**. In this study, although the first- and fifth-minute Apgar scores were unfavorable in 12 patients (16.9%) and 4 patients (5.6%), respectively, most neonates had normal Apgar scores (10.9) and the mean neonatal weight was in the normal range, and only one neonate death was observed. Also in the current study, the preterm birth rate was 18.1%, and the neonatal admission rate at NICU was 16.25%. In similar studies, the rate of low birth weight (LBW) in the neonates of affected women showed an increase that was associated with neonatal complications such as infant mortality **(20, 21)**. The reason for this difference can be that most of the infants in our study were near term, which has led to normal weight and Apgar scores and lower neonatal mortality in them because birth weight is an important predictor of neonatal mortality **(22)** and maternal disease alone cannot lead to adverse neonatal consequences. Studies on neonatal complications in the United Kingdom, the United States, and Ireland showed that maternal Covid-19 disease during pregnancy did not show a significant association with neonatal complications **(23, 24)**. In this regard, the results of our study showed that the increase in infant mortality due to maternal infection with Covid-19 did not occur, but the relationship between maternal disease severity and neonatal complications was statistically significant (P<0.001). In 42.3% of pregnant women with severe clinical symptoms, poor neonatal outcome was observed. This result was similar to that of the previous study (18), but the Irish study found no association between maternal disease severity and preterm birth **(24)**. Among neonatal complications, the most reported outcome in patients in the current study was preterm birth. This result is in line with similar studies in the world **(24-28)**. The preterm birth rate in the current study (18.1%) was higher than the nationally reported rate of non-infected pregnant women (10%) **(29, 30)**. The small number of samples in our study and the lack of comparison of preterm birth rates in non-infected pregnant women in the same time period made it difficult to draw definitive conclusions about changes in preterm birth rates after maternal infection. In this regard, the comparison of pregnant women with Covid-19 (25%) with non-infected pregnant women (10%) in the same period of time in the country has shown an increase in the number of preterm births **(31)**.

The NICU admission rate in the current study was 16.25%, compared to previous studies **(8, 9)**, indicating an increase in neonatal admission of pregnant women with Covid-19 **(32)**. On the other hand, neonatal hospitalization in NICU was associated with more neonatal complications in general, while the neonatal mortality rate in NICU in Iran was estimated at 11.4%, based on a review study, and the most common causes of these deaths were LBW and pre-maturity **(33)**.

Regarding fetal outcomes in affected women, the results showed that the rate of FGR was 1.9% and fetal complications were 1.2%, which was not higher than the rate of these indicators in the general population of pregnant women **(14)**. There are not enough studies to investigate the effect of Covid-19 on abortion or congenital anomalies **(34)**, so further studies are needed to conclude. A comparative study in this field in Iran showed that there was no significant difference in these cases between pregnant women with and without Covid-19 **(31)** and in another study fetal outcomes such as abortion, intrauterine growth restriction, and congenital anomalies were rare **(23)**. Contrary to our results, the rate of intrauterine death in a study in the United Kingdom and the United States showed a slight increase, which was not significant compared to the same rate in the general population **(23)**. Albeit, it is important to note that most of the infected women were identified or hospitalized in the third trimester, which means that the mothers 'infection was not followed up in the first or second trimester. So, comparing and interpreting the results of maternal infection in the first and second trimesters is difficult. There is a hypothesis that placental villi are more susceptible to infection in the first and second trimesters **(35)**.

The results of the study showed that the majority of deliveries were performed by cesarean section (82.5%). The most common cause of cesarean section was repeated cesarean section (43.2%) and this can be justified due to the high rate of cesarean section in Iran **(36)**. However, 35.8% of the causes of cesarean section in infected women had other reasons, which could be related to the management and decision-making process for delivery in infected and hospitalized pregnant women. A review study in this field showed that the increase in cesarean section rate in infected women could be due to aggressive management of labor and also the decrease in support for infected pregnant women during vaginal delivery due to staff fear of contracting the Covid-19 **(15)**. Our study also showed that there was no statistically significant relationship between disease severity and type of delivery ($p = 0.412$). In fact, this rate of the cesarean section did not occur due to the direct complications associated with Covid-19 infection, which is in line with the results of the study of Vaezi et al. **(14)**. An increase in the rate of cesarean section in infected women was seen in previous studies **(15, 37)**, which was due to the presence of severe symptoms of the disease **(13, 19)**. The difference in this result may be due to the greater number of adverse maternal outcomes (maternal admission to the ICU) in their study, which directly affects the type of delivery. Also, the lack of a significant relationship between the severity of symptoms and the rate of cesarean section in our study could be due to the high rate of repeated cesarean section **(6)** and clinical guidelines for choosing the type of delivery in women with Covid-19 are different **(38)** but a large study in the United States found that vaginal delivery in these women did not increase the risk of infants infection **(3)**. Therefore, the decision to give birth should be made based on maternal and fetal indications.

Current information on the impact of Covid-19 disease on pregnancy and prenatal outcomes is based on reports from developed countries, which makes it difficult to compare the results with the current study. Also, the results of the current study have been done on the population of pregnant women with moderate and severe disease and have not considered pregnant women with mild disease who have been treated on an outpatient basis.

Conclusion

In conclusion, the results of the present study showed that an increase in poor maternal, fetal and neonatal outcomes has been seen particularly in pregnant women with severe symptoms, so careful care is still recommended for affected pregnant women to reduce fetal, neonatal, and maternal complications.

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Ethical consideration

The present study was approved by the Guilan University of Medical Sciences (IR.GUMS.REC.1399.016). Before data collection, the researchers informed the participants about the objectives of the research and started the study after obtaining written consent from participants.

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Conflict of Interest

The authors report no conflict of interest regarding publication of this paper.

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