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The Incidence Rate of COVID-19 and its Relationship with Maternal and Neonatal Outcomes among Pregnant Women during Iran's First and Second Waves: A Multicenter Cohort Study in Tehran

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ABSTRACT

Background & aim: COVID-19 infection may adversely affect pregnancy outcomes. We aimed to assess the incidence rate of the COVID-19 virus and its effect on maternaland neonatal outcomes.

Methods: This was a cohort study in which a number of health-care centers in Tehran province were randomly selected, and all pregnant women referring to these centers were screened for COVID-19 from April 2020 to July 2020. Out of 15520 pregnant women, 263 individuals infected with COVID-19, who were followed until delivery. To collect the data, a demographic and obstetric characteristics questionnaire and a maternal and neonatal outcome checklist were used. Data analysis was done by SPSS version 22 using the Chi-square test, independent t-test, and logistic regression model.

Results: The incidence of COVID-19 among participants was 17 per 1000 (95% CI: 15-19). Women with a higher BMI (OR = 1.198, CI =1.003-1.431, P = 0.047) and lower blood oxygen level (OR= 0.886, CI: 0.808-.970, P=.009) were more likely to have adverse pregnancy outcomes. Preterm labor (18.3%) was the most common outcome of pregnancy, followed by stillbirth (0.8%), ICU admission (3.0%), maternal mortality (1.1%), need to mechanical ventilation (1.5%) and preeclampsia 1(0.38). Regarding neonatal outcomes, neonatal COVID-19 was seen in 1.9% of cases, NICU admission in 15.2%. Neonatal mortality without COVID-19 in 2.3%. The majority of neonates with complications were male (29.1% vs. 21.5%, (P= 0.002).

Conclusion: Pregnant women had a lower COVID-19 incidence rate than the general population, but when infected, they were at risk for poor maternal and neonatal outcomes.

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Introduction

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The outbreak of an infectious respiratory disease which later came to be known as COVID-19 first appeared in Wuhan, China, in late December 2019. This disease was later announced by the World Health Organization (WHO) as the sixth major public health emergency worldwide, threatening the whole planet (1). The current epidemic of SARS-CoV-2 has wreaked havoc on people from all walks of life, and pregnant women are no exception, with those diagnosed with this disease increasing in number (2). Following the rapid increase in the rate of people affected with this virus around the world, the first cases of this infection in Iran were confirmed in February 2020 (3).

The incidence of COVID-19 and pneumonia is higher in people with weakened immune systems, which includes people with underlying diseases, the elderly, and pregnant women (4). There is evidence that the risks of maternal mortality, stillbirth, and preterm labor are higher among women with viral pneumonia caused by viruses such as the Middle East Respiratory Syndrome (MERS), influenza A, Severe Acute Respiratory Syndrome (SARS), and H1N1 (5).

Pregnant women are vulnerable to COVID-19 due to certain pregnancy conditions. They are also more likely to contract infections, develop severe illness, and die from respiratory diseases (6). The following physiologic changes during pregnancy have been reported as predisposing factors for more severe illness among pregnant women compared with non-pregnant women: increased heart rate and oxygen consumption, reduced lung capacity, and a shift away from cell-mediated immunity (7). Providing safe care for pregnant women and newborns is the top priority for health providers and policy makers (8). Although the prevalence of COVID-19 among asymptomatic pregnant women is low and estimated to be 3%, the rate of hospitalization, ICU admission, and mechanical ventilation is higher among these women as opposed to non-pregnant women. However, the risk of death among this population is similar to that of non-pregnant women (9). Furthermore, given fetal tolerance against hypoxemia and acidosis, these complications can result in preterm labor (10).

Despite a number of studies conducted on COVID-19 in pregnant women around the world, there is still a paucity of information about this disease in Iranian pregnant women. Therefore, the purpose of this research was to investigate the incidence rate of the COVID-19 virus and its effect on maternal and neonatal outcome among pregnant women during Iran's first and second waves.

Materials and Methods

This cohort study involved screening and follow up of COVID-19 infection among pregnant women referring to outpatient public health centers in Tehran province between April 15, 2020, and July 26, 2020. Pregnant women in Iran receive all prenatal/postpartum care offered free of charge at public health centers.

Pregnant women were eligible to participate in the study if they had basic literacy and were suspected of or diagnosed with COVID-19. Women who were not willing to participate were excluded from the study.

Since no previous study was available about the prevalence of COVID-19 infection among pregnant women, the sample size was estimated to be 15,520 pregnant women, assuming a 95% confidence interval, P=0.5, the limit of error (0.01), and design effect (1.5). The following formula was used for the calculation of sample size:

$$n \geq \frac{(z_{1-\frac{\alpha}{2}})^2\, p(1-p)}{d^2}$$

In total, 153 public health centers (37 affiliated to Tehran University, 59 to Iran University, and 57 to Shahid Beheshti University) were selected using cluster random sampling in each university. All pregnant women were selected based on their information recorded in SIB. SIB, a Persian backronym meaning *apple* in Persian, is the Integrated Electronic Health System in Iran, storing demographic and administrative health data of nearly 72 million Iranians out of the 81 million population (around 90% coverage). A similar percentage of health-care centers are covered by this system.

Phone calls were made with the pregnant women whose numbers were obtained from SIB. All pregnant women (n = 15,520) referring to these centers were screened for COVID-19. At each collaborating center, a midwife health provider asked pregnant women questions inquiring about demographic information, their medical history, recent symptoms associated with COVID-19, and exposure to COVID-19. Participants were selected based on the hospital protocols for COVID-19 diagnosis and treatment in outpatient and inpatient settings in Iran. Patients who, according to the protocols, were suspected of or diagnosed with COVID-19 were enrolled; otherwise, they were excluded. At least one of the following clear epidemiological history criteria had to be met in order to define suspected cases of COVID-19: (1) a history of travel to or residency in communities with COVID-19 cases within two weeks before the onset of the disease; (2) a history of contact with people with COVID19 within 14 days before the onset; and (3) a history of contact with people suffering from fever or respiratory symptoms living in places where COVID-19 is prevalent. Furthermore, the presence of at least one of the following clinical manifestations was also taken into account: (1) fever and/or respiratory symptoms; (2) anosmia or ageusia; (3) myalgia; (4) imaging features of COVID-19; and (5) normal or diminished white blood cells in early stages of disease and a diminished lymphocyte count. If the patients had a clear epidemiological history and clinical manifestations, they were invited to participate in the study. Afterwards, laboratory tests including either RT-PCR or chest CT scan were used to confirm cases with suspected COVID-19. After identifying all pregnant women affected with COVID-19, we followed them up until delivery. Nasopharyngeal samples of neonates were taken immediately after birth or within 48 hours after birth. Written informed consent was obtained from all participants. To collect the data, a demographic and obstetric characteristics questionnaire, and a maternal and neonatal outcome checklist were used. The demographic and obstetric questionnaire inquired about age, education, occupation, ethnicity, body mass index, monthly income of the family, residence, type of insurance, gestational age, blood group, symptoms of COVID-19, medical conditions, laboratory findings, chest CT scan, and treatment plan. The validity of this questionnaire was confirmed through content and face validity methods. The maternal and neonatal outcome checklist included information about mode of birth, pregnancy outcomes (e.g., preterm labor, stillbirth, ICU admission, mechanical ventilation, maternal mortality, etc.), admission to NICU, neonatal COVID-19 infection, Apgar score, neonate's weight, and neonatal mortality. The validity of this checklist was assessed through content and face validity.

The data were obtained using patient medical records available in hospitals or health centers and were recorded in the questionnaire and the checklist. The completion of checklists lasted 30 min on average.

In case of incomplete data, a phone call was made to the participants. All data were obtained and reviewed by three of the research team members (ZM, FH, and MSH).

The primary outcomes were maternal mortality, delivery mode, preterm labor, ICU admission, stillbirth, and mechanical ventilation. The secondary outcomes were neonatal mortality, infection of newborns with COVID-19, NICU admission, neonatal weight, and 1^{st}- and 5^{th}-minute Apgar score.

Incidence and outcomes were expressed as frequency and percentage with a 95% confidence interval. The chi-square test and Fisher's exact test were used to compare categorical data. All analyses were done using IBM SPSS version 22.

To compare quantitative outcomes, the independent t-test was used. Analysis of outcome-related factors was done using univariate and multivariable logistic regression models. $P < 0.05$ value was considered statistically significant in all tests.

Results

Of all 15520 pregnant women included in the screening, 263 cases were identified with confirmed COVID-19. The records of these women were assessed during the first and second COVID-19 waves in Iran. In this study, 10(3.8%), 80(30.4%), and 173(65.8%) out of the 263 pregnant women were in their first, second, and third trimesters of pregnancy, respectively.

Table 1. Demographic characteristics of the participants

All patients (n=263)	
Variables	**Mean ±SD/ N (%)**
Age, years	29.63 ± 5.97
Gestational age (wks)	30.86±7.37
BMI (kg/m2)	26.36±3.8
Vitamin D (ng/ml)	22.73±14.03
Parity, mean (SD)	1.89±7.49
History of abortion	31(11.8)
Twin pregnancy	6(2.2)
Medical problems	
Diabetes	13(4.9)
Hypothyroid	58(22.1)
Others	37(14.1)
Healthy	155(58.9)
Nationality	
Iranian	228(86.7)
Afghan	35(13.3)
Income status	
Good	28(10.6)
Moderate	175(66.5)
Poor	60(22.8)
Educational attainment	
Illiterate	19(7.2)
High school Diploma	106(64.7)
University degree	74 (28.1)
Residence	
Urban	250(95.1)
Rural	13(4.9%)
Employment status	
Housewife	235(89.4)
Employed	28(10.6)
Blood group	
A	91(34.4)
B	59 (22.6)
O	92(35.3)
AB	19(7.3)
Symptoms of COVID-19	
Cough	25(9.5)
Sore throat	26(9.8)
Dyspnea	7(2.6)
Fever	16(6.08)
Olfactory	21(7.9)
A combination of symptoms	151(57.41)
Asymptomatic	17(6.4)

Participants were aged 13-44 years, and the mean ± SD of gestational age was 30.86 ± 7.37. Most cases were of Iranian nationality, followed by Afghans. Mean± SD of vitamin D level and body mass index (BMI) was 22.73 ± 14.04, and 26.3 ± 3.83, respectively. Only 15(5.7%) of the patients had unintended pregnancy. Common comorbidities among affected women were hypothyroidism, gestational diabetes, hypertension, and depression. The commonest symptoms observed at the onset of the disease were coughing 25(9.5%), sore throat 26(9.8%), olfactory disorders 21(7.9%), and fever 16(6.08%). In total, 17(6.4%) of the patients were asymptomatic. The blood group of the majority of the participants infected with Covid-19 was O+. Five women had twins, and one had a triplet pregnancy (Table 1).

The incidence of COVID-19 was 16.94 per 1000 pregnant women (95% CI 15-19). A total of 460 women were suspected of having COVID-19, of whom 263 (57.17) were confirmed based on the RT-PCR test. The incidence of COVID-19 was calculated according to the following formula: 263/15520=0.01694 * 1000=16.94.

Maternal and Neonatal Outcomes

Table 2 presents the maternal and neonatal outcomes. The majority of the infected women underwent caesarean section (C/S). Overall, adverse maternal and neonatal outcomes were observed in 65(24.7%) mothers and 53(20.2%) neonates. In 45(17.1%) of the cases, adverse outcomes were seen in both the mothers and their neonates.

Table 2. Maternal and neonatal outcomes of the participants

Variables	All patients (263) N (%)
Maternal and Neonatal adverse outcomes	
Maternal adverse outcomes	65(24.7)
Neonatal adverse outcomes	53(20.2)
Maternal and neonatal adverse outcomes	45(17.1)
Delivery mode	
Vaginal delivery	69(26.2)
C/S	194(73.8)
Emergency C/S	54(20.53)
Pregnancy outcomes	
Preterm labor	48(18.3)
Stillbirth	2(0.8)
ICU admission	8(3.0)
Mechanical ventilation	4(1.5)
Maternal mortality	3(1.1)

Healthy	198(76.4)
Neonatal outcomes	
COVID-19	5(1.9)
NICU admission	40(15.2)
Neonatal mortality without COVID-19	6(2.3)
COVID-19 and NICU	2(0.8)
COVID-19 and neonatal mortality	1(0.3)
Healthy	210(79.8)
Fetal weight, mean	3108.34±664.29
Intended pregnancy	
Yes	248(94.3)
No	15(5.7)
Type of care	
Outpatient	201(76.42)
Hospitalization	62(23.57)
Length of hospital stay (day)	6.4(1.00-37)

While 62(23.57%) of the participants were hospitalized, most of them received outpatient care. The mean length of hospital stay was 6.4 days.

Preterm labor 48(18.3%) was the most common outcome of pregnancy among the studied women, followed by stillbirth 2(0.8%), ICU admission 8(3.0%), preeclampsia 1(0.38), maternal mortality 3(1.1%), and mechanical ventilation 4(1.5%).

The COVID-19 test was performed on neonates whose mothers were positive for the disease in their second and third trimesters 178(67.7%). Neonatal outcomes were neonatal mortality without COVID-19, 6(2.3%), COVID-19 positive 5(1.9%), and NICU admission 40(15.2%). The blood group of the neonate's mother infected with COVID-19 were O+, B-, and A+. All five neonatal mortalities without COVID-19 were male.

Table 3. Comparison of demographic, maternal, and neonatal characteristics between the two groups of women with and without adverse events

Variable	With Adverse pregnancy outcomes n=73	Without Adverse pregnancy outcomes n=190	P-Value
	Mean (SD)/ N (%)	**Mean (SD)/ N(%)**	
Age (years)	30.24 (7.21)	29.4 (5.7)	0.325*
Gestational Age (week)	28.06 (7.97)	31.93 (6.85)	<0.001*
Parity	2.13(1.12)	2.11(1.09)	0.853*
BMI (kg/m2)	27.18 (4.38)	26.05 (3.56)	0.032*
Vitamin D (ng/ml)	21.62 (15.15)	23.30 (13.46)	0.468*
Sao_2	91.8 (7.16)	95.07 (2.9)	<0.001*
Fetal weight	2499.3 (820)	3332.7 (413)	<0.001*
Apgar at 1 min	7.2 (2.1)	8.9 (0.2)	<0.001*
Apgar at 5 min	8.3 (2.4)	9.9 (0.12)	
Delivery mode			
Vaginal delivery	9(13.04)	60(87)	0.002**
C/S	64(32.98)	130(68.1)	
Emergency C/S	29(53.7)	25(46.2)	0.002**
Fetal sex			
Male	39(29.1)	95(70.9)	0.002**
Female	26(21.5)	95(78.5)	
Length of hospital stay	8.1(8.7)	4.5(2.4)	0.021*
History of medical problems	45(61.64)	80(42.11)	0.664**

*Data analyzed using independent t-test **Data analyzed using Chi-square test or Fisher's exact test

We had three maternal deaths. These mothers were in their 31st, 38th, and 40th weeks of gestation. All of them underwent C/S. Except for the baby of a pregnant mother who contracted the infection in her 31st week, the other two babies were alive and well obtaining good Apgar scores, and were negative for COVID-19.

Finally, the clinical characteristics and outcomes of pregnant women with and without adverse pregnancy outcomes were compared (Table 3). No significant difference was observed between the two groups in terms of their demographic information such as age, blood group, educational attainment, comorbidities, income status, insurance coverage, and symptoms (P=0 .430).

Adverse pregnancy complications were more likely to be observed among women in their second trimester, and they had a significantly lower mean gestational age compared with the group without adverse pregnancy outcomes (28.06 ±7.97 vs. 31.93 ±6.85, P= 0.002). Furthermore, patients with higher BMI had more complications (P=0 .032). The two groups were different in terms of vitamin D levels, yet the difference was not statistically significant.

The group with adverse outcomes had significantly lower mean fetal weight as opposed to the group without adverse outcomes (2499.3±820.4 vs. 3332.7±413.5, P< 0.000).

Table 4. The association of factors with maternal and neonatal adverse effects

Variables	Adjusted Model					
	B	S. E	P-value	Odds Ratio	95% CI	
Body mass index	0.180	0.091	0.047	1.198	1.003	1.431
Sao_2	-0.122	0.047	0.009	0.886	0.808	0.970

Significantly lower 1st-minute and 5th-minute Apgar scores were observed among neonates of women with adverse outcomes (p<0.000). Most neonates in the group with complications were male (29.1% vs. 21.5%, p= 0.002).

Four pregnant women with twin pregnancies were infected with COVID-19 (three in their 3rd trimester, and one in her 2nd trimester). Three of these women had preterm delivery after preterm pre-labor rupture of membrane (PPROM), and all of the twin neonates were admitted to the NICU. A woman with triplet pregnancy was affected with COVID––19 at the 28th week of gestation and delivered her babies at the 30th week of gestation. Two of these fetuses were females who died, but the third fetus who survived was a boy infected with COVID-19 who was hospitalized in the NICU for 27 days.

For a better understanding of the relationship of predictive factors such as age, gestational age, parity, BMI, sao_2, hospital stay, and history of chronic diseases with maternal and neonatal adverse effects, the logistic regression model for multivariate analysis using the backward method (unadjusted and adjusted) was used (Table 4). Women with higher BMI (OR = 1.198, CI =1.003-1.431, P=0.047) and low blood oxygen (OR= 0.886, 95% CI: 0.808-0.970, P=0.009) were more likely to show maternal and neonatal adverse effects, respectively.

Discussion

This study provided a summary of the clinical characteristics and incidence rate of COVID-19among pregnant women in Tehran province. Particularly, we compared the clinical features in women with and without adverse outcomes in this study. Up to the time of writing this manuscript, there have been three peaks of COVID-19 in Tehran province, with the most severe infection being in the third peak. In the present study, the incidence rate of COVID-19 in pregnancy was 16.94 per 1000. Our data collection was done in the period between the beginning of the first peak and the end of the second peak in Tehran, Iran.

Poustchi et al. (2020) showed that according to a population-based cross-sectional study, the seroprevalence of COVID-19 across 18 cities of 17 provinces in Iran was estimated to be 17·1% (95% CI 14·6–19·5). Also, in the general population, the seroprevalence estimate in Tehran was 16.3% (13·5–19·5) (11). Compared to this study, our results show that the prevalence of COVID-19 in pregnancy during the first and second waves of this disease in Iran was lower compared to the general population. Pregnant women are exposed to a higher risk for infectious diseases such as COVID-19 owing to their suppressed immune system and physiological changes associated with pregnancy, which will lead to more adverse outcomes (12).

In the present study, most infected women were in their 2nd or 3rd trimester of pregnancy, but women who had complications were more likely to be in their 2nd trimester. The onset of

COVID-19 was accompanied by common symptoms such as coughing, sore throat, and olfactory disorders. Symptoms such as fever and dyspnea were less common, and some of the women were asymptomatic. In this study, compared to the national rate of preterm delivery and C/S rate, the rate of preterm birth and C/S was relatively higher (13-15).

In two large cohort studies, the overall preterm delivery rates of pregnant women with COVID-19 in the United States were found to be higher than those of women without COVID-19 infection, and the national prevalence of preterm delivery (16) Also, overall C/S rates among COVID-19 mothers were similar to those in mothers not infected with COVID-19 and the overall C/S rate in the United States. The higher rate of C/S in the present study may be due to the fact that the rate of C/S in Iran is higher than that in the United States, and it involves more than half of total births (17).

Although the risks of preterm birth, preterm rupture of membranes, and abnormal fetal heart rate patterns may be increased due to fever and hypoxemia, patients not suffering from severe respiratory disease also experience preterm births (18). Based on our results, stillbirth was one of the adverse events observed in COVID-19 pregnant patients. Results of a study on stillbirth rates of pregnant women with confirmed or suspected COVID-19 from 12 countries (the UK and the US) were almost similar to our data (19).

Evidence has shown that although the risk for COVID-19 infection is not increased due to pregnancy, the clinical course of COVID-19 seems to deteriorate in pregnant women compared to their age-matched non-pregnant counterparts (20-21). In the current study, most women affected with COVID-19 infection did not need hospitalization, which is similar to the results of other studies (22).

The maternal death rate was 1.1% in the present study. Results of a systematic review showed a higher mortality rate among COVID-19 pregnant women compared with their otherwise healthy counterparts (23). A number of other studies reported that the maternal death ranged from 0.15 to 0.80% in pregnant women infected with COVID-199 (19, 21, 24), which seems to be higher than the rate observed in pregnant women not infected with the disease. This could be explained by the uncertainty of patients with no or mild symptoms of COVID-19 and the relatively small rate of mortality (19).

The present study showed that most of the babies born to mothers with COVID-19 were in good condition at birth. According to the report of the Centers for Disease Control and Prevention (CDC), in a large population of pregnant women with laboratory-confirmed COVID-19 infection, the neonatal infection with COVID-19 was higher than what we found in our results (16), which could be attributed to the larger sample size compared with the present study. In addition, all of the neonates in the present study did not undergo a PCR-RP test. In the uterus, transmission typically occurs through a hematogenous pathway, but sometimes it occurs in an ascending way. Studies have reported low rates of viremia in mild COVID-19 patients, but severe cases of the disease have been associated with higher rates of viremia (25). Despite the insufficient evidence, it seems that utero transmission is not common (18).

In our study, the total number of neonatal mortalities was seven of which only one was due to COVID-19. In a Schwartz study in Iran, the number of mortalities among neonates affected with COVID-19 was reported to be two cases (26). The study included 19 neonates infected with COVID-19, and the neonatal mortality was calculated for these 19 cases, but in our study, there were five neonates infected with COVID-19. According to a systematic review, both COVID-19 positive and negative women had a similar incidence of neonatal mortality (24).

Our results showed significantly lower fetal weight and 1st – and 1st- and 5th-minute Apgar scores among women with adverse pregnancy outcomes.

Also, the result of this study showed insufficient serum 25(OH) D levels in both groups with and without adverse events. Low mean serum 25(OH) D levels were reported in countries such as Spain, Italy, and the United Kingdom where the course of COVID-19 was severe (27). Another study found significantly lower levels of 25(OH) D in COVID-19 patients compared with the accepted cut-off values (28). This result was consistent with our findings.

According to our results, women with higher BMI and low levels of blood oxygen were at a greater risk of maternal and neonatal adverse effects. Evidence indicates the association of overweight and obesity with more severe COVID-19 (29). Restrictions, such as house quarantine, reduced social activities, fears and concerns about fetal health and development as well as exposure of pregnant women to overeating (30).

Generally, it seems that pregnant women are at risk for maternal and neonatal outcomes and are regarded as a vulnerable group, so improving adherence to preventive measures against COVID-19 among pregnant women is required. (30-31)

Most of the pregnant women in the present study were in the third trimester, and the findings we obtained here could be used for comparison with maternal and neonatal outcomes in pregnant women in the first or second trimesters. These findings could not only serve as guidelines for prenatal care management for COVID-19 women but also be used as information resources for policy-making bodies. Additionally, we recommend that researchers investigate the long-term effect of COVID-19 infection in women and their neonates. We also had two additional findings that are worth considering: First, in the group with complications, most of the neonates were male, and second, most affected participants had blood group O+.

That this study was conducted in the entire Tehran province and different ethnic groups participated in it is its main strength. However, it is limited in that its findings cannot be generalised to other provinces in Iran. In addition, only pregnant women admitted to public and governmental hospitals were screened in this study, and we did not assess those in private hospitals. It is suggested these factors be examined in future studies

Conclusion

The incidence rate of COVID-19 among pregnant women was lower than that of the general population during the first and second waves of this disease, and the second trimester of pregnancy was characterized by an increased risk of adverse pregnancy outcomes. Also, pregnant women affected by COVID-19 showed adverse outcomes such as preterm birth, the need for hospitalization, maternal mortality, and C/S. The neonatal adverse events included admission to NICU, decreased birth weight, and low Apgar scores. Women with a higher BMI and lower blood oxygen had more adverse pregnancy outcomes. In a few neonates, COVID-19 was transmitted vertically.

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Conflicts of interest

Authors declared no conflicts of interest.

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