Journal of Midwifery & Reproductive Health

JMRH.mums.ac.ir

Pregnancy Outcomes in Women With COVID-19: A Case-Control Study in Iran

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ARTICLE INFO

Article type:
Original article

Article History:
Received: 08-Feb-2021
Accepted: 13-Nov-2022

Key words:
COVID-19
Pregnancy Outcomes
Iran

ABSTRACT

Background & aim: Little is known about the effects of COVID-19 on pregnancy outcomes. The present study was performed to investigate maternal and perinatal outcomes in pregnant women affected by COVID-19.

Methods: This case-control study was conducted on 264 pregnant women, including 132 infected (case group) and 132 uninfected pregnant women with COVID-19 (control group), using a retrospective record review design and matched sampling in three hospitals in Hamadan Province, Iran.Pregnant women with a positive COVID-19 test were identified through the registration system for COVID-19 in the health centers. The two groups were matched in terms of gestational age and maternal age. Data were collected from February 2020 to October 2021 using a questionnaire consisting of demographic and obstetric data, maternal and perinatal outcomes, and information about COVID-19 detection and treatment. Data were analyzed by SPSS software (version 22).

Results: A high percentage of the case group lived in urban areas (p=0.026). In the case group, newborn hospitalization and death were significantly higher (p=0.032). No differences were observed between the two groups in other maternal or perinatal outcomes. Although there was one maternal death, two HELLP syndromes, and two cases of pregnancy cholestasis in the case group, however, they were not statistically significant.

Conclusion: Although most maternal and perinatal outcomes were not statistically significant in COVID-19 pregnancies, some important outcomes, especially maternal death, occurred only in the case group. More evidence is needed to confirm whether COVID-19 can negatively affect pregnancy outcomes.

▶ *Please cite this paper as*:
Alibakhshi F, Javadnoori M, Ghanbari S. Pregnancy Outcomes in Women with COVID-19: A Case-Control Study in IRAN. Journal of Midwifery and Reproductive Health. 2023; 11(2): 3664-3671. DOI: 10.22038/JMRH.2022.63589.1844

Introduction

With the outbreak of COVID-19 in December 2019 in Wuhan, China, the World Health Organization declared it a pandemic in March 2020 (1). Numerous studies all over the world started to work on it, and sometimes contradictory results were presented (1-4). Although in many cases, COVID-19 causes very mild symptoms, it can be severe in people who are vulnerable in terms of their medical conditions. Pregnancy is a unique situation in which the mother and fetus cooperate peacefully. Physiological changes that occur during pregnancy, although favorable for the fetus, make mothers susceptible to infectious pathogens; the COVID-19 pandemic challenges pregnancy (2). Although coronavirus can affect anyone, pregnant women may be more susceptible to the virus due to physiological and immune changes during pregnancy (5).

Previous research on the 2019 novel coronavirus disease (COVID-19) outbreak was based on information from the general public.

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Data are scarce on pregnant women with COVID-19 (6). The consequences of coronavirus on pregnant women and their infants are unclear (7). Previous studies have shown that pregnant women are at higher risk for developing viral infections such as acute respiratory syndrome, middle east respiratory syndrome, influenza, stillbirth, preterm delivery, respiratory distress, intrauterine growth restriction, and ICU hospitalization (8, 9). The coronavirus pandemic is a common stress factor, even for non-infected people. Studies show that pregnant women experience significant increases in stress, anxiety, and depression during the coronavirus outbreak (10). These high stress levels may adversely affect pregnancy, intrauterine growth, and birth weight, even among healthy and non-infected pregnant women. Accordingly, the rate of preterm delivery and intrauterine growth restriction, especially low birth weight, may increase (11). Studies during the coronavirus epidemic show that most cases of infection occur in the third trimester of pregnancy (12, 13). According to the studies, mothers with coronavirus are at increased risk for preterm delivery, miscarriage, premature rupture of membranes, preeclampsia, cesarean section, fetal distress, intrauterine death, ICU hospitalization, and preterm delivery, which are the most common adverse outcomes of pregnancy (14-16).

There is little knowlege about the effect of COVID-19 on pregnancy outcomes. Further studies are required in this field. Therefore, more research is needed in this field, because the behavior of this virus is still unknown, particularly its impact on pregnancy outcomes. The present study was performed to compare the pregnancy outcomes in pregnant women infected with coronavirus and non-infected women in Hamadan province, Iran.

Materials and Methods

This case-control study was conducted on 132 pregnant women with covid-19 as a case group and 132 uninfected pregnant women as a control group using a retrospective record review design and matched sampling.The retrospective record review is a research design in which obtaining prerecorded data are reviewed to answer the research question (17). Because of this, hospital records from February 20, 2020, to October 30, 2021, in three hospitals in Hamadan Province, Iran, were used to collect data. In the study, we included pregnant women between the ages of 18 and 35 who did not have any other diseases. Pregnant women with a positive COVID-19 test who met the inclusion criteria were considered the case group. In order to find pregnant women whose COVID-19 test came back positive; their information was taken from the COVID-19 registration system in the health centers. Women who met the inclusion criteria were enrolled. They were then tracked to identify which hospital in Hamadan these women used to give birth. The information about pregnancy outcomes was extracted from the hospital records using a checklist. The checklist contained items about demographic data, obstetric history, maternal and perinatal outcomes, and information about COVID-19 detection and treatment.

The results of the pregnancy were recorded. These results included abortion, gestational age, amniotic fluid volume, gestational diabetes, preterm rupture of membranes, intrauterine growth restriction, type of delivery, preeclampsia, fetal distress, Apgar score, morphological abnormality in the newborn, birth weight, stillbirth, and neonatal death. Any other maternal or neonatal outcomes were also recorded. Women who were in the hospital for a vaginal birth without a history of COVID-19 infection at the same time were chosen for the control group. They were matched with the case group in terms of gestational age and the mother's age. Pregnancy outcomes were compared between the two groups.

The ethics code for this study is IR.AJUMS.REC.1400.207. It was approved by the Research Ethics Committee at Ahvaz Jundishapur University of Medical Sciences. The study was conducted as a retrospective analysis of medical records, and the patients' identities were kept confidential.

Data were analyzed by SPSS (version 22) and the Chi-square test. $P<0.05$ was regarded as statistically significant.

Results

In total, the information of 264 pregnant women included in this study. Demographic

characteristics of the participants were shown in Table 1.

Table 1. Comparing the two groups in terms of demographic and obstetrics data

Variable	Case group (N=132) Number (%)	Control group (N=132) Number (%)	Test statistics	P-value
Place of residence				
Urban	92(69.7)	73(55.3)	7.27	0.026
Rural	39(29.5)	59(44.7)		
Educational level				
High school	70(53.0)	68(51.5)		
Diploma	51(38.6)	50(37.9)		
Associate degree	10(7.6)	5(3.8)	8.15	0.086
Bachelor	1(0.8)	8(6.1)		
Master	0(0.0)	1(0.8)		
Occupational status				
Employee	7(5.3)	10(7.6)		
Self-employment	0(0.0)	1(0.8)	1.59	0.465
Jobless	125(94.7)	121(91.7)		
Addiction				
Yes	1(0.8)	0(0.0)	1.01	0.989
No	131(99.2)	132(100.0)		
BMI				
Underweight	0(0.0)	2(1.5)		
Normal	37(28.0)	41(31.1)	4.69	0.196
Overweight	56(42.4)	62(47.0)		
Fat	39(29.5)	27(20.5)		
Blood group				
A+	39(29.5)	33(25.0)		
A-	5(3.8)	4(3.0)		
B+	28(21.2)	32(24.2)		
B-	7(5.3)	5(3.8)	4.41	0.729
O+	43(32.6)	39(29.5)		
O-	3(2.3)	6(4.5)		
AB+	6(4.5)	12(9.1)		
AB-	1(0.8)	1(0.8)		
Gravidity				
1	44(33.3)	58(43.9)		
2	57(43.2)	46(34.8)	4.72	0.347
3	19(14.4)	18(13.6)		
≥4	12(9.1)	10(7.6)		
Parity				
0	54(40.9)	65(49.2)		
1	59(44.7)	49(37.1)	2.27	0.521
2	17(12.9)	15(11.4)		
3	2(1.5)	3(2.3)		
Previous abortion				
0	105(79.5)	112(84.8)		
1	22(16.7)	16(12.1)	1.37	0.706
2	2(1.5)	2(1.5)		
3	3(2.3)	2(1.5)		
Previous type of delivery				
NVD	54(69.2)	45(67.2)	0.071	0.859
C/S	24(30.8)	22(32.8)		

* Chi-square test

The homogeneity of case and control groups in terms of the demographic variables was investigated using the Chi-square test. Among the demographic factors, only the place of residence was significantly different between the two groups, which showed that more people in the case group were urban dwellers. In terms of the other demographic variables, no significant difference was observed between the case and control groups.

Maternal outcomes are shown in Table 2. Maternal outcomes included gestational age, amniotic fluid volume, HELLP syndrome, DIC, gestational cholestasis, gestational diabetes, preeclampsia, type of delivery, and perineal laceration. The chi-square test showed that the two groups were homogeneous in terms of maternal outcomes.

Table 2. Comparison of two groups in terms of maternal outcomes

Variable	Case group (N=132) Number (%)	Control group (N=132) Number (%)	Test statistics	P-value*
Gestational age				
Term	113(85.6)	116(87.9)	0.296	0.717
preterm	19(14.4)	16(12.1)		
Amniotic fluid volume				
Normal	126(95.5)	130(98.5)		
Oligohydramnios	6(4.5)	2(1.5)	2.06	0.282
Polyhydramnios	(0.0)	0(0.0)		
Pregnancy cholestasis				
Yes	2(1.5)	0(0.0)	2.01	0.498
No	130(98.5)	132(100.0)		
HELLP syndrome**				
Yes	2(1.5)	0(0.0)	2.01	0.498
No	130(98.5)	132(100.0)		
DIC				
Yes	1(0.8)	0(0.0)	1.00	0.997
No	131(99.2)	132(100.0)		
Gestational Diabetes				
Yes	12(9.1)	12(9.1)	0.00	1.00
No	120(90.9)	120(90.9)		
PROM***				
Yes	31 (23.5)	28 (21.2)	0.196	0.768
No	101(76.5)	104(78.8)		
Perineal condition				
Episiotomy	29(40.3)	35(43.8)		
Healthy perineum	43(59.7)	44(55.0)	1.16	0.741
Grade e3 Perineal tear	0(0.0)	1(1.3)		
Type of delivery				
Natural Vaginal Delivery	71(53.8)	80(60.6)	1.25	0.320
Cesarean section	61(46.2)	52(39.4)		
Preeclampsia				
Yes	3(2.3)	2(1.5)	0.204	0.995
No	129(97.7)	130(98.5)		

* (Chi-square test) ** Hemolysis,elevated liver enzymes , and low platelets ***Premature of Membranes

Neonatal outcomes, including malformations, intrauterine growth restriction, fetal distress, abortion, and stillbirth, are shown in Table 3. Neonatal outcomes were significantly different between the two groups (P= 0.032). According to the results, 81% of newborns in the case group and 92% in the control group were discharged in complete health. Also, 17.7% of the newborns in the case group and 8.7% in the control group were hospitalized in the neonatal

ward, and one newborn died after birth. One case of syndactyly (in the case group), one case of Down syndrome, and one case of clubfoot (in the control group) were observed. Four intrauterine deaths occurred in the case group, and one in the control group.

Out of 132 patients in the case group, 24.2% were asymptomatic and 75.8% had symptoms. The most common symptoms in patients with COVID-19 included cough (22%), myalgia (19.7%), fever (18.9%), and a lack of smell and taste (15.2%). Less common symptoms included shortness of breath (9.8%), lethargy (8.3%), headache (5.3%), vomiting (5.3%), runny nose (4.5%), and sore throat (4.5%).

In the case group, 96.2% were identified by PCR test, 2.3% by CT lung scan, and 1.5% by both methods. Additionally, 30 patients were hospitalized for COVID-19 treatment, which used oxygen therapy, antibiotic treatment (Keflin, Ceftriaxone, azithromycin, vancomycin, Meropenem, Clindamycin, and Gentamicin), anticoagulant treatment (Enoxaparin, Heparin), Vitamin C, Pantoprazole, Ondansetron, Dexamethasone, Remdesivir, Famotidine, and Hydroxychloroquine.

Among the hospitalized women, 27 (90%) were discharged in good general condition (18 were hospitalized for less than three days and 9 for more than three days). Also, two women (7.6%) were discharged with personal satisfaction, and one case (3.3%) of maternal death was found.

Table 3. Comparison of two groups in terms of neonatal outcomes

Variable	Case group (N=132) Number (%)	Control group (N=132) Number (%)	Test statistics	P-value*
Neonatal outcome				
Discharge with a good status	106(81.5)	119(92.2)		
Hospitalized	23(17.7)	10(7.8)	6.87	**0.032**
Death after birth	1 (0.8)	0(0)		
Apgar score				
More than 7	126(95.5)	127(96.2)	0.095	0.785
Less than 7	6(4.5)	5(3.8)		
Sex of newborn				
Female	63(47.7)	67(50.8)		
Male	69(52.3)	64(48.5)	1.31	0.623
ambiguous	0(0.0)	1(.08)		
IUGR**				
Yes	3(2.3)	2(1.5)	0.204	0.989
No	129(97.7)	130(98.5)		
Fetal distress				
Yes	28(21.1)	18(13.6)	2.63	0.144
No	104(78.8)	114(86.4)		
Abortion				
Yes	0(0.0)	2(1.5)	2.01	0.498
No	132(100.0)	130(98.5)		
Morphological abnormality				
Yes	1(0.8)	2(1.6)	0.32	0.998
no	131(99.2)	130(98.4)		
Birth weight				
≥2500	121(91.7)	123(94.6)	0.89	0.465
<2500	11(8.3)	7(5.4)		
Stillbirth				
Yes	4(3.0)	1(0.8)	1.83	0.370
No	128(97.0)	131(99.2)		

*Chi-square test ** Intrauterine growth restriction

One case of maternal death that occurred in the case group involved a 36-year-old primigravida woman at 35 weeks of gestation who presented with symptoms of shortness of breath, headache, and cough. She was admitted for treatment and died in the hospital due to cardiopulmonary arrest. A cesarean section was performed to save the fetus, and the male newborn was born with first- and fifth-minute Apgar scores of 1/10 and 4/10, respectively. The baby died after birth. Two cases of cholestasis of pregnancy occurred in the case group; they were infected with coronavirus at 26 and 35 weeks, and cholestasis of pregnancy was diagnosed at 37 and 39 weeks.

There were two cases of HELLP syndrome and one case of DIC in the case group.

Discussion

According to the results of this study, most maternal and perinatal outcomes were not statistically significant in COVID-19 pregnancies. However, some important outcomes, like maternal death, which only occurred in the case group, may be clinically important. Although one case of maternal death, two cases of HELLP syndrome, two cases of cholestasis, and one case of DIC occurred only in the case group, although they were not statistically significant.

In the present study, most patients in the case group were urban dwellers. The study by Li et al. (2020) showed that demographic variables were not significantly different between the two groups (16). Some previous studies reported no significant difference in maternal weight and height between the two groups (18). However, a meta-analysis reported that a significant number of pregnant patients with COVID-19 were obese, with a mean BMI of 32.1 kg/m2 (19).

In our study, there was no increase in preterm delivery in the group of pregnant women positive for COVID-19. Similarly, in a prospective cohort study in New York, there was no increase in the rate of preterm delivery in pregnant women positive for COVID-19 (20). In another case-control study (2020), women with COVID-19 had significantly more premature births. They concluded that COVID-19 is not directly responsible for this rise in premature births. PROM, or placenta abruption, is one of the issues that contribute to it. (16). The study performed in Iran showed a more than twofold increase in the probability of preterm delivery in women affected by COVID-19 (1). A systematic review and meta-analysis in 2021 showed that COVID-19-positive pregnant women had a higher rate of preterm birth due to ruptured membranes and spontaneous labor. However, it was not clear whether COVID-19 could be a direct cause of preterm birth (21). The results of the present study replicated the findings of two studies in Iran that found no difference between the two groups in terms of the amniotic fluid index and PROM rates (1, 15).

In the present study, there was no difference between COVID-19-positive women and non-positive women in terms of preeclampsia rate, but Savasi et al. (2020) reported the opposite results (22). The reason for this contradiction is probably that women with underlying diseases were not included in the present study, whereas they studied women with underlying diseases, and the risk of preeclampsia is higher in women with underlying diseases.

In the present study, no difference was observed between the two groups in terms of the rate of cesarean delivery. In a case-control study, all of the women with COVID-19 had cesarean deliveries. COVID-19 was seen as a reason to have cesarean deliveries (16). Despite the recommendation of experts to suggest vaginal delivery for these women, in a meta-analysis study, the prevailing method of delivery was cesarean section (21). Concerns about the mother-to-baby transmission of the virus during childbirth seem to have been overblown.

According to the results of the present study, newborn hospitalization, and death significantly increased in the case group. The higher percentage of newborn hospitalizations can be justified by the policies of infant protection. This policy was also reported in some previous studies (1, 16, 22).

The findings of the present study didn't show an increase in the incidence of low birth weight in Covid-19-positive mothers. In two previous studies, most neonates born to COVID-19-positive women had a normal weight of 2500-4000 gr Since COVID-19 appears as an acute infection, it seems that it does not affect birth weight if it occurs at the end of pregnancy.

The results of this study were similar to the results of several other studies that had been done before. There is no difference in outcomes like the Apgar score and fetal distress (1, 16, 20, 21).

In this study, there were four cases of intrauterine death and three cases of intrauterine growth restriction. These results were not statistically significant, which was consistent with what other studies had found (1, 20, 21, 23, 24). Although intrauterine death was not statistically significant, it is clinically significant, i.e., intrauterine death in COVID-positive women is about four times that of non-positive women.

The results of the present study showed that COVID-19 causes mild respiratory symptoms in most pregnant women, and the most common symptoms included: cough, myalgia, and fever, which reflected the findings of some previous studies. A retrospective study showed that the most common symptom in pregnant women positive for COVID-19 is fever, followed by cough (23). Also, in a systematic review, the most common symptoms included fever, cough and sore throat (25).

One of the strengths of the present study was the larger sample size compared to previous case-control studies. The findings of this study may aid physicians and patients in the effective management of COVID-19 infection during pregnancy. One of the limitations of the present study was that our analysis was performed on the recorded data retrospectively. Data collected through this process, especially during the covid-19 pandemic crisis, are not necessarily accurately recorded. On the other hand, given the limited capacity of the health system during the crisis, some covid-19 cases may have been missed. Future studies with a cohort design may provide more accurate and reliable findings.

Conclusion

The findings of the present study showed that pregnancy outcomes such as gestational age, gestational diabetes, preeclampsia, fetal distress, Apgar score, birth weight, intrauterine growth restriction, and stillbirth were not significantly different between COVID-19-infected pregnant women and non-infected women. Although most maternal and perinatal outcomes were not statistically significant in COVID-19 pregnancies, some important outcomes, especially maternal death, which occurred only in the case group, may be clinically important. More evidence is needed to confirm whether COVID-19 can negatively affect pregnancy outcomes.

Acknowledgement

This article was extracted from the M.S. thesis of the first author in midwifery. The authors would like to express their gratitude to Hamadan University of Medical Sciences, Hamedan, Iran, for their collaboration in this research and to Ahvaz Jundishapure University of Medical Sciences, Ahvaz, Iran, for their financial support.

Conflicts of interest

The authors declared no conflicts of interest.

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