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Intrauterine Growth Restriction and other pregnancy complications following covid-19 infection

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ABSTRACT

Background: The WHO, reported world widespread coronavirus disease (COVID-19) as an international public health emergency. Pregnancy is associated with immunological changes that may make women susceptible to COVID-19. The present study was conducted to clarify the impacts of the pandemic on intrauterine growth restriction (IUGR) and other pregnancy complications.

Material & methods: In a historical cohort study, COVID-19-positive cases who were hospitalized and a subgroup of Intensive Care Unit (ICU)-admitted (severe) cases were compared with those who had no history of COVID-19 infection, regarding IUGR and other complications of pregnancy.

Results: Among 1010 pregnant women enrolled in the study, 43 (4.3%) had a history of hospitalization due to COVID-19 (including 28 ICU-admitted severe cases) through pregnancy and the other 967 cases who had no history of infection were compared. In comparing COVID-19 with non-COVID-19 groups, IUGR, and preterm labor were more frequent in the COVID-19 group (16.3% versus 6.9%) and (51.2% versus 19.9%), respectively. Also, the cesarean section rate was higher (75% versus 55.3%) and the low APGAR score was more frequent (16.3% versus 3.3-3.7%)

Conclusion: Complications of COVID-19 infection in pregnancy such as IUGR, preterm labor, higher rate of cesarean section, and low APGAR score might make pregnant women more vulnerable to the COVID-19 pandemic and probable future versions of viral pandemics.

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Keywords: COVID-19; Growth Restriction; Preterm; Pregnancy

Introduction

The first cases of COVID-19 pneumonia from a novel coronavirus appeared in Wuhan, China in December 2019 [1,2]. The coronavirus disease (COVID-19) has spread rapidly worldwide as a result of infection with acute respiratory syndrome SARS-CoV-2 [3]. The WHO reported this condition as an International Public Health Emergency [1,4]. This disorder has also affected pregnant women and pregnancy outcomes [5,6]. Pregnancy is associated with immunological changes that may make women susceptible to COVID-19 [7]. Despite the 2019 COVID-19 pandemic and extensive studies in this field, the impact of SARS-CoV-2 on the developing fetus is not completely clear. Physiological changes in the mother during pregnancy have a significant effect on the coagulation, immune, respiratory, and cardiovascular systems of the fetus and may have positive or negative effects on the course of the disease (COVID-19). Studies have shown that pregnant women may be vulnerable to the adverse effects of COVID-19 [8]. Definitive evidence of Mother-to-child vertical transmission of SARS-CoV infection is not available in the available data, but some pregnancy complications such as premature birth, risk of miscarriage, intrauterine death, intrauterine growth restriction (IUGR), low birth weight, spontaneous abortion, and mortality have been reported through mothers with COVID-19 [8,9]. Some studies have also shown that maternal COVID-19 can affect fetal oxygen supply and lead to placental insufficiency, IUGR, or fetal death [8]. Children with IUGR are at greater risk for long-term problems such as short stature, metabolic syndrome, type 2 diabetes, insulin resistance, and cardiovascular diseases [10,11]. Studies also show that these children may have puberty disorders, reproductive function, and adrenal secretion disorders. During pregnancy, several viral infections are known to increase the risk of fetal malformations, including IUGR, without significant long-term effects on the health of the offspring [11]. Considering the long-term effects of IUGR on a person's life Infected during the fetal period and the lack of sufficient information regarding the relationship between COVID-19 and IUGR in the studies, the present study was conducted to clarify the uncertainties in this field.

Materials and method:

The study is a historical cohort and was conducted under the supervision of the Obstetrics and Gynecology Department of Imam Hossein Hospital in Tehran, Iran including pregnant cases who visited for labor pain between 2019 and 2021 during the COVID-19 pandemic. Since the study was conducted in a university hospital, an informed consent form was obtained from all patients for the use of information. Patients with intrauterine growth restriction risk factors such as addiction, chronic hypertension, and other systemic diseases, including pre-eclampsia were excluded from the study. Those with a history of mild COVID-19 infection who didn't need to be hospitalized (mild cases) were excluded from the study. Age, height, weight, BMI, type of delivery, gravid, para, live children, gestational age, date of delivery, alcohol use, cocaine use, addiction, chronic blood pressure, preeclampsia, diabetes, lupus, Chronic kidney disease, epilepsy, drug history, history of IUGR, previous birth weight, multiple pregnancy, definite anomaly, APGAR score, history of infection with COVID-19 followed by hospitalization, and/or hospitalization in ICU, symptoms of cough, fever, weakness, shortness of breath, and taking Remdesivir in positive history cases were extracted from the patients documented data in each group and was entered in the questionnaire for each patient. We defined moderate disease as hospitalized cases and severe cases as a subgroup of ICU-admitted COVID-19-infected patients. We compared COVID-19-positive hospitalized patients(moderate) and the subgroup of COVID-19-positiveICU-admitted(severe) patients with those who had no history of COVID-19 infection regarding IUGR. IUGR criterion was considered less than the 10^{th} percentile birth weight of newborns.

This study was in accordance with the ethical issues for human subject research and confirmed by the Shahid Beheshti University of Medical Sciences by an ethical committee (IR.SBMU.RETECH.REC.1402.176). Informed consent was obtained from all subjects. The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Statistical analysis:

Data were analyzed with Software Package for the Social Sciences (SPSS, version 19.0). After checking the normality of continuous variables, an independent t-test was used to compare continuous variables Chi-square test or Fisher exact test was used to compare dichotomous variables Binary logistic regression analysis was done to detect independent predictors of IUGR. The significant level was set at 0.05.

Results:

Among 1010 pregnant women who entered the study, 43 (4.3%) were moderate or severe and hospitalized due to COVID-19 (COVID-19 group). In these cases, the cough was the most frequent symptom (72.1%) followed by fever (65.1%), weakness (63.4%), and dyspnea (62.8%). Two groups (moderate to severe COVID-19 cases versus non-COVID-19 subjects) were not significantly different in terms of gestational diabetes (28.6% versus 26.3%), preeclampsia (2.3% versus 4.3%), and chronic hypertension (7.0% versus 6.1%), respectively, P>0.1. No one in the COVID-19 group had diseases of SLE, chronic renal disease, and

epilepsy. Three (0.3%) subjects from the non-COVID-19 group had SLE, 8 (0.8%) had chronic renal disease, and 11 (1.1%) had epilepsy, P>0.1. In the COVID-19 group, 2.3% were smokers, 2.3% had an addiction, and no one used alcohol or cocaine. The frequency rate of smoking, alcohol use, cocaine use, and addiction were 1.4%, 0.3%, 0.5%, and 2.8% in the non-COVID-19 group, respectively (P>0.1). Only two women in the non-COVID-19 group were on warfarin, 2 had a history of IUGR, and 5 had multiple pregnancies.

Twenty-eight out of 43 cases (65.1%) of the COVID-19 group were admitted to the ICU. The median (range) of hospitalization days was 5 (1–20) and ICU days were 5 (1–38). COVID-19 and non-COVID-19 groups were compared. Subgroup comparison of the COVID-19 ICU-admitted cases with non-COVID-19 cases is done, as well. Both COVID-19 and COVID-19 ICU admitted subgroups were older than the COVID-19 group, P<0.05.

Neonates of the COVID-19, ICU-admitted subgroup of severe cases had significantly lower birth weights in comparison to the non-COVID-19 cases. IUGR (less than 10 percentile rate adjusted by gestational age) was more frequent in the COVID-19 group (16.3%) and ICU-admitted subgroup of severe cases (21.4%) than in the non-COVID-19 group (6.9%). The mean gestational age at delivery was significantly lower in moderate COVID-19 (35.0 ± 4.5) and ICU-admitted COVID-19 subgroup (33.4 ± 4.7) in comparison with the non-COVID-19 cases (38.0 ± 2.6), P<0.001. Preterm labor rate was 51.2% and 71.4% in the COVID-19 group and ICU admitted subgroup, which was significantly higher than non-COVID-19 group (19.9%), P<0.001. less than 7 Apgar score at 5 min and less than 9 in 10 min rate were 16.3% in the COVID-19 group and 25% in the ICU admitted subgroup, which was significantly higher than the non-COVID-19 group (3.3-3.7%). The Cesarean section rate was 75.0% in the COVID-19, 84.6% in the ICU admitted subgroup of severe cases versus 55.3% in the non-COVID-19 group, P=0.014 and P=0.003, respectively (Table 1).

Table 1: Comparison of maternal and obstetric characteristics in the non-COVID-19 group with the COVID-19 group and with the subgroup of severe COVID-19 ICU admitted cases.

	Non-COVID 19 (n=967)	**COVID 19 (n=43)**	**PV***	**COVID-19 ICU Admitted (n=28)**	**PV***
Maternal age (year)	29.2 (± 6.3)	31.5 (± 5.9)	0.020†	31.8 (± 5.6)	0.034†
BMI	29.5 (± 5.0)	30.0 (± 4.9)	0.592†	30.8 (± 5.3)	0.216†
Nulliparous	317 (32.8)	11 (25.6)	0.322x	7 (25.0)	0.384x
Previous birth weight	3160.3 (± 549.0)	3095.4 (± 495.5)	0.570†	3076.9 (± 501.9)	0.588†
Gestational wk. at delivery	38.0 (± 2.6)	35.0 (± 4.5)	<0.001††	33.4 (± 4.7)	<0.001††
Preterm labor	192 (19.9)	22 (51.2)	<0.001 x	20 (71.4)	<0.001 x
Apgar score at 5 min <7	36 (3.7)	7 (16.3)	0.002 xx	7 (25.0)	<0.001 xx
Apgar score at 10 min <9	32 (3.3)	7 (16.3)	0.001 xx	7 (25.0)	<0.001 xx
Birth weight (gram)	3076.5 (± 636.3)	2441.4 (± 495.5)	<0.001††	2191.3 (± 937.9)	<0.001††
IUGR	67 (6.9)	7 (16.3)	0.032 xx	6 (21.4)	0.013 xx
C/S	488 (55.3)	30 (75.0)	0.014 x	22 (84.6)	0.003 x

Data are shown as mean (+ SD) or frequency (%). GDM: Gestational Diabetes Mellitus, BMI: Body Mass Index, IUGR: Intra Uterine Growth Retardation, C/S: Cesarean /Section, * Versus Non-COVID-19. † Based on independent-samples t-test, Levene's Test for Equality of Variances, P>0.05, Equal variances assumed. †† based on the independent-sample t-test, Levene's Test for Equality of Variances, P<0.05, Equal variances are not assumed. x Chi-Square Test, xx Fisher's Exact Test

In the binary logistic regression analysis, the chance of IUGR in the COVID-19 group was 2.6 times (95% CI: 1.1–6.1), and in the ICU-admitted subgroup was 3.7 times (95% CI: 1.4–9.3) more than in the non-COVID-19 group (Table 2). Also, the chance of preterm labor in the COVID-19 group was 4.2 times (95% CI: 2.3–7.9), and in the ICU-admitted subgroup was 10.1 times (95% CI: 4.4–23.3) more than in the non-COVID-19 group (Table 3).

Table 2: The odds ratio (95%CI) of IUGR in binary logistic regression analysis

Group	**Odds Ratio (95% CI)**	**PV**
Non-COVID 19	Reference	0.026
COVID 19	2.6 (1.1 – 6.1)	
Non-COVID 19	reference	0.007
ICU admitted COVID-19	3.7 (1.4 – 9.3)	

CI: Confidence Interval, ICU: Intensive Care Unit

Table 3: The odds ratio (95%CI) of preterm labor in binary logistic regression analysis

Group	**Odds Ratio (95% CI)**	**PV**
Non-COVID 19	Reference	<0.001
COVID 19	4.2 (2.3 – 7.9)	
Non-COVID 19	Reference	<0.001
ICU admitted COVID-19	10.1 (4.4 – 23.3)	

CI: Confidence Interval, ICU: Intensive Care Unit

Discussion:

SARS-CoV-2 infection is an inflammatory process that is presented with proinflammatory changes such as increased Th2 cell-associated cytokines and the increase of IgG and IgA has been observed about 2 weeks after infection with human coronavirus which affects multiple organs and the systems of the body

[1,3]. The effect of COVID-19 on pregnancy outcomes is not exactly specified [8]. Due to changes in the immune and cardiorespiratory system during pregnancy, pregnant women and newborns may be more susceptible and vulnerable to COVID-19 infection [9].

In the group of pregnant women under our investigation, in positive-COVID-19 hospitalized pregnant women the average birth weight was lower. Furthermore, Preterm labor and cesarean section also were more common in people with moderate and severe COVID-19 infection (hospitalized and ICU-admitted COVID-19-infected patients). Previous studies have also demonstrated that preterm labor was higher in COVID-19-infected women compared to non-infected women [4].

Some studies have also shown that in pregnant patients, the fetus's oxygen supply can be affected by COVID-19 and may lead to IUGR(8). The studies that were conducted during the previous SARS and MERS pandemics on pregnancy showed an increased risk of IUGR [5,8,11]. In the results of the present study, the percentage of IUGR is also significantly different in moderate and severe COVID-19 infection (hospitalized and subgroup ICU-admitted COVID-19 infected patients) compared with non-COVID-19 women. Therefore, surveillance for IUGR in women with SARS-CoV-2 infection is recommended because IUGR is often observed in ongoing pregnancies with SARS-CoV-2.

Preterm labor depends on various factors such as a history of previous preterm birth, multiple gestations, black race, and infection [12,13]. Any condition such as infections that can weaken the immune system can lead to preterm labor [12]. As previous studies show, in the present study, the chance of preterm labor was higher in the COVID-19 group [14]. New information about the maternal-fetal interface and the interactions between the maternal immune system and the placenta might explain these findings [12].

Cesarean section(C/S) is associated with a higher risk of uterine rupture, ectopic pregnancy, abnormal placentation, stillbirth, and preterm labor. Also, there is a higher rate of maternal mortality and morbidity and short-term and long-term negative effects on the life of the fetus in C/S than vaginal birth [15]. The current study showed that cesarean section was more in the COVID-19 group and considering the many complications of the cesarean section that were mentioned, COVID-19 can also be troublesome in this regard. Apgar score of the fetus can be related to uteroplacental function, and because COVID-19 is a systemic and immunological disease, it can leave its inflammatory effects everywhere, including in the placenta and the Uteroplacental unit. In this study, it was seen that COVID-19 has an effect on the Apgar score of the fetus and in this way, it can have a negative effect.

So finally, the fetus is affected by this inflammatory process, and COVID-19 can affect the pregnancy outcome by increasing the risk of IUGR, preterm labor, lower APGAR score, and cesarean section. This study revealed that pregnant women are more vulnerable to COVID-19, and if there are new strains of COVID in the future, special attention is necessary to protect pregnant women.

The limitation of our study was the retrospective pattern of the study, Since the pandemic had subsided at the time of designing the study, we could not plan a prospective type of study.

Conclusion

In conclusion, the viral pandemic of COVID-19 affects pregnant women through the occurrence of IUGR (defined by less than 10 percentile), preterm labor, and cesarian section. Therefore, more precautions during pregnancy might be recommended to avoid SARS-2-Covid infections and probably new versions of it and even new viral pandemics.

Ethical Issue

This study was in accordance with the ethical issues for human subject research and confirmed by the Shahid Beheshti University of Medical Sciences by an ethical committee (IR.SBMU.RETECH.REC.1402.176). Informed consent was obtained from all subjects.

Conflict of Interests

There was no conflict of interest in this study.

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