Journal of International Medical and Biological Sciences
ISSN: 2617-8885
International Peer Reviewed
JIMBS
Original Article

Effect of COVID-19 on Maternal and Neonatal Pregnancy Outcomes among Iraqi Patients

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Received: February 2022, Accepted and Published online: April, 2022

Abstract:

Currently, in relation to the effect of COVID-19 on pregnancy, there are more questions than certainties about the real impact of COVID-19 on pregnant women. Studies are updated and often contradict each other. There is no evidence to suggest that pregnant women with COVID-19 have higher morbidity than affected non-pregnant women. However, a sufficient number of pregnant women have not yet been studied to allow appropriate inferences to be made. Therefore, this case-control study aimed to assess the effect of COVID-19 on maternal and neonatal pregnancy outcomes among Iraqi patients. We included 82 pregnant women infected with COVID-19 and compared them to 82 healthy pregnant women as control group. Results revealed that Infection with COVID-19 had a significant effect on pregnancy outcome, infected women were more likely to have higher incidence rates of adverse perinatal outcomes in both mothers and the newborns.

***Keywords**: SARS-Cov-2, COVID-19, Epidemiology, complications, Pregnancy Outcomes*

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***Citation**: Rasha N. Al-Baaj, Effect of COVID-19 on Maternal and Neonatal Pregnancy Outcomes among Iraqi Patients. JIMBS 2022; 8 (2):144*

1. INTRODUCTION

During December 2019, in China, Wuhan city, first case of SARS-CoV-2 was reported and manifested as severe acute respiratory syndrome. It has been shown that the virus can penetrates through the respiratory tract mucous membrane to the peripheral blood and infects target organs (lungs, gastrointestinal tract, cardiovascular system, kidneys), the cells of which express angiotensin-converting enzyme. CoV-2 virus binds by surface spikes formed by the S-Proteins to ACE-2 protein on the cell-membranes of the macroorganism. By integrating into the cell, the virus replicates, which leads to the release of new virions from the infected cell, affecting target organs, which induces the development of a local and systemic inflammatory response. COVID-19 is diagnosed based on real-time PCR by detection its RNA in the swab samples from the nasopharynx from patients, regardless the clinical symptoms (1–4).

Recent observations have shown that majority of pregnant women are more likely to have mild form of the disease or been asymptomatic. However, about 3% of pregnant women with COVID-19 require intensive care (5). COVID-19 infection diagnosed during pregnancy can adversely affect the fetus.

Preliminary data indicate that infection with COVID-19 during first trimester of pregnancy did not lead to an increase in the thickness of the nuchal zone of the fetus, or to the development of congenital anomalies, or to developmental delay, and did not lead to increase the risk of miscarriage compared with other trans placental infections, such as the Zika virus (6). At the same time, clinical observations of pregnancies against the background of SARS-CoV-2 infection at later stages were described, ending in premature birth and even perinatal fetal, and mother death (7,8) It is not completely clear whether premature termination of pregnancy is a complication of this infection or is due to obstetric tactics aimed at early delivery of sick women. Most literature sources devoted to the analysis of the course of a new coronavirus infection in pregnant women, women in labor and newborns assessed the somatic status and morphological and functional characteristics of children delivered by infected women at delivery (8–11). Given the hypercoagulation observed in patients with COVID-19, perinatal complications in children are likely due to impaired fetoplacental perfusion and/or possible thrombotic changes in the mother, vasculopathy, decreased placental barrier function, and inflammatory changes in it (12).

It has been noted that in pregnancies occurring against the background of SARS and MERS, intrauterine growth retardation (IUGR) is often recorded(12). The frequency of IUGR during pregnancies occurring against the background of a new coronavirus infection did not exceed the general population data (13).

The changes inherent to pregnancy make pregnant women a population more susceptible to suffering from severe forms of the disease, although studies in this regard show an evolution of the disease similar to that reported in non-pregnant women. Premature delivery, especially by caesarean section, is more recommended in this group of pregnant women because it avoids complications and reduces the risk of mortality for the mother and the newborn. In addition to premature birth, some scientific studies acknowledge the increase in the frequency of preeclampsia, spontaneous abortion and perinatal death. Therefore, all pregnant women with a positive diagnosis for COVID-19 must remain under continuous surveillance during pregnancy. The objective for this study was to assess maternal and neonatal outcomes in pregnant women with COVID-19 compared to non-infected pregnant women

2. PATIENTS AND METHODS

A Retrospective, Case-Control observational, and analytical study carried out during the period from July 2021 to February 2022,

Patients (cases)

including 82 Iraqi pregnant women treated in two maternal and childcare centers, in whom the antibody test for COVID-19 was performed and was positive.

Inclusion criteria :

Singleton pregnant women aged 18-35 years with with a positive report of the rapid antibody test.

Exclusion criterion:

1. Positive diagnosis with only IgM.
2. Medical records with incomplete information.
3. Pregnant women with gestational hypertension or DM.
4. Pregnant women with chronic diseases.
5. History of abortion
6. History of premature labor

7. History of other complication during pregnancy such as Preeclampsia, antepartum hemorrhage, postpartum hemorrhage.

8. Women underwent assisted reproductive procedures.

9. Women with signs and symptoms of spontaneous miscarriage or ectopic pregnancy.

Controls:

A total of 82 pregnant women without COVID-19 with negative PCR tests and have no history of infection during the pandemic. Controls were apparently healthy with no any comorbidities or complications during their pregnancy. They were almost matched to cases regarding the demographic characteristics and obstetrical history. Similar exclusion criteria to that of cases were applied for controls

Data collection

The data collection technique was documentary review and the data collection form (questionnaire) used was prepared by the researchers after rigorous review of literatures and previous studies published globally. The questionnaire was reviewed and validated by three specialist obstetricians who have a high degree of specialization in gynecology and obstetrics. The main source of information was the clinical history of pregnant women. However, the questionnaire was included three sections:

1) General characteristics, made up of four items (age, level of education, obstetric history ; gravidity, parity, abortion, previous mode of delivery, number of cesarean sections and number of children).

2) Maternal outcomes, made up of six items (preeclampsia, threatened preterm birth, hemorrhage in the second half of pregnancy, premature rupture of membranes, preterm birth, and cesarean section).

3)Positive diagnosis of COVID-19 according to the antibody test, composed of only one item where the pregnant woman is categorized according to the test report.

Acute infection was considered to be the coexistence of positive both IgM with IgG, and past infection when only IgG positive. The test used was the One Step test for Novel Coronavirus (2019-nCov) IgM/IgG Antibody (Colloidal Gold) manufactured by Daan Gene Co of Sun Yat-Sen University in China. Its sensitivity is greater than 91% and specificity greater than 97%, according to the list of rapid tests of the General Directorate of Public health of the Iraqi Ministry of Health

Definitions:

For purpose of this study, the following definitions were applied

Preeclampsia : Arterial hypertension associated with proteinuria, in women with more than 20 weeks of pregnancy (14). The operational definition of the study was the diagnosis of preeclampsia established by an obstetrician-gynecologist and recorded in the clinical history.

Preterm labor: multifactorial syndrome that leads to the onset of labor between 22 to 36 weeks 6 days of gestation. For the study, its operational definition consisted of the diagnosis of preterm birth by a gynecologist with the establishment of the fact in the clinical history (15)..

Caesarean section: surgical intervention performed to extract the fetus by medical indication or electively by the pregnant woman. For the study, its operational definition consisted of the programming of cesarean section for medical indication recorded in the clinical history (16).

Low Apgar score: Apgar score of the newborn below 7 at the first or 5th minutes after birth.

Stillbirth: prenatal, or antenatal the fetus dies before birth, in utero (starting from 28 weeks of pregnancy); during childbirth, or intranatal: the fetus dies directly during childbirth; and postpartum, or postnatal - the fetus is born with a heartbeat , but it dies due to the fact that it does not establish extrauterine respiration (17) .

Data analysis

The data analyzed using the statistical package for social sciences (SPSS) version 25 program. The general characteristics were presented descriptively in a frequency table that compared pregnant women with acute infection and past infection. For the inferential analysis, the variable COVID-19 infection and maternal complications of a qualitative and dichotomous nature were considered. To determine the association between the variables considering the unilateral approach that the frequency of complications in pregnant women with acute infection is greater than that of pregnant women with past infection, Fisher's exact test was applied, considering a significance level of 5%. The strength of association between the variables was determined by calculating the odds ratio (odd ratio) with a 95% confidence interval.

3. RESULTS

A total of 82 pregnant women with COVID-19 (cases) and 82 apparently healthy pregnant women as control group were enrolled in this study, both studied groups were almost matched and not significantly different in their baseline characteristics, including age, body mass index (BMI) and obstetrical history, gestational age at infection (P > 0.05). The mean gestational age at delivery was significantly lower in COVID-19 cases compared to controls, 37.8 ± 1.6 weeks vs. 38.6 ± 0.8 weeks, respectively, (P<0.05), (Tables 1 & 2).

Comparison of maternal pregnancy outcomes of the studied groups revealed that cesarean section mode of delivery was more frequent among COVID-19 cases than controls, 63% vs. 21.5%, respectively, (P<0.05). Miscarriage also more frequent in cases than controls, (P<0.05). Preeclampsia reported in 20.7% of cases and 8.5% of controls, maternal death occurred in 2.4% of COVID-19 cases vs. none among controls, however, the differences did not reach the statistical significance, (P>0.05), (Table 3).

As shown in (Table 4), generally, adverse neonatal outcomes were more frequent in COVID-19 cases than controls, adverse neonatal pregnancy outcomes; fetal distress, stillbirth, preterm labor, lower Apgar score at 1 and 5 minutes and admission to neonatal intensive care unit were significantly more frequent in cases than controls, (P<0.05). Despite that neonatal mortality rate was higher in cases, 3.7%, compared to 1.2% in controls, but the difference was statistically insignificant, (P>0.05), (Table 4).

Laboratory parameters of COVID-19 cases are shown in (Table 5)

Regarding the severity , the disease was mild in 47 (57.3%) cases, moderate in 22 (26.8%) and severe in 13 cases (15.9%), (Table 6).

Regarding the predictors of adverse maternal and neonatal outcomes, it had been found that older maternal age, infection at earlier stage of pregnancy (lower gestational age at infection), higher white blood cells (WBCs) count, COVID-19 infection and severe disease form were significantly associated with higher frequency of adverse maternal outcomes, however, more severe form of disease was the stronger predictors with an odds ratio (OR) of 4.860, (Table 7).

The significant predictors of adverse neonatal outcomes among COVID-19 cases were older maternal age, obesity, lower gestational age at infection and severe disease form which is the stronger predictor (OR= 3.825), (Table 8).

Table 1. Baseline characteristics of the studied groups

Variable		COVID-19 cases (n=82)		Controls (n=82)		P. value
		No.	%	No.	%	
Age (year)	≤ 20	22	26.8	24	29.3	0.820 ns
	21 - 30	45	54.9	41	50.0	
	> 30	15	18.3	17	20.7	
	Mean age (SD)	26.1 (5.5)		25.7 (5.2)		
BMI category	Normal	28	34.1	32	39.0	0.810 ns
	Overweight	29	35.4	27	32.9	
	Obese	25	30.5	23	28.0	
	Mean (SD) (kg/m²)	28.2 (5.4)		28.7 (5.1)		
Gravidity	1 - 2	40	48.8	44	53.7	0.807 ns
	3 - 4	29	35.4	27	32.9	
	5 - 6	13	15.9	11	13.4	
Parity	Nulliparous	28	34.1	26	31.7	0.818 ns
	1 - 2	33	40.2	37	45.1	
	≥ 3	21	25.6	19	23.2	
Previous cesarean section		18	22.0	16	19.5	0.700 ns

SD: standard deviation of mean, ns: not significant

Table 2. Gestational age at infection and at delivery of the studied groups

Variable	COVID-19 cases (n=82)		Controls (n=82)		P. value
	Mean	SD	Mean	SD	
Gestational age at infection	28.4	4.2	28.7	4.0	0.881 ns
Gestational age at delivery	37.8	1.6	38.6	0.8	0.001 sig

SD: standard deviation of mean, ns: not significant, sig: significant

Table 3. Comparison of maternal pregnancy outcomes of the studied groups

Variable		COVID-19 cases (n=82)		Controls (n=82)		P. value
		No.	%	No.	%	
Mode of delivery	NVD	27	37.0	62	78.5	0.001 sig
	CS	46	63.0	17	21.5	
Preeclampsia	Yes	17	20.7	7	8.5	0.401 ns
	No	65	79.3	75	91.5	
Miscarriage	Yes	9	100.0	3	100.0	0.018 sig
	No	0	0.0	0	0.0	
Maternal mortality	Survived	79	96.3	82	100.0	0.401 ns
	Died	2	2.4	0	0.0	

ns: not significant, sig: significant, CS: cesarean section

Table 4. Comparison of Neonatal pregnancy outcomes of the studied groups

Variable		COVID-19 cases (n=82)		Controls (n=82)		P. value
		No.	%	No.	%	
Fetal distress	Yes	9	11.0	2	2.4	0.044 sig
	No	73	89.0	80	97.6	
Stillbirth	Yes	2	2.4	0	0.0	0.029 sig
	No	80	97.6	82	100.0	
Preterm Labor	Yes	10	12.2	3	3.7	0.024 sig
	No	72	87.8	79	96.3	
Apgar score 1 min	> 7	58	70.7	72	87.8	0.007 sig
	< 7	24	29.3	10	12.2	
Apgar score 5 min	> 7	70	85.4	78	95.1	0.032 sig
	< 7	12	14.6	4	4.9	
Admission to NICU	Yes	14	17.1	4	4.9	0.012 sig
	No	68	82.9	78	95.1	
Neonatal mortality	Survived	79	96.3	81	98.8	0.311 ns
	Died	3	3.7	1	1.2	

ns: not significant, sig: significant, NICU: neonatal intensive care unit

Table 5. Laboratory parameters of COVID-19 cases

Parameter	Frequency	Percent
Leukocytosis > 11,000 cell/ml	35	42.7
Elevated NLR > 3	63	76.8
Elevated D-Dimer	43	52.4
Elevated CRP	55	67.1
Elevated Serum ferritin	29	35.4

Table 6. Severity of disease among COVID-19 cases

Severity	Frequency	Percent
Mild	47	57.3
Moderate	22	26.8
Severe	13	15.9
Total	82	100.0

Table 7. Predictors of adverse maternal pregnancy outcomes among COVID-19 cases

Variable	OR	P. value
Maternal age	1.416	0.022 sig
Obesity	1.014	0.382 ns
Gravidity	0.924	0.617 ns
Parity	0.829	0.319 ns
Lower gestational age at infection	2.14	0.011 sig
Previous cesarean section	1.137	0.244 ns
WBCs count	1.932	0.037 sig
NLR	1.832	0.017 sig
Severity of disease	4.860	0.001 sig

ns: not significant, sig: significant, WBCs: white blood cells , NLR: neutrophil to lymphocyte ratio, OR: odds ratio

Table 8. Predictors of adverse neonatal pregnancy outcomes among COVID-19 cases

Variable	OR	P. value
Older maternal age	1.841	0.030 sig
Obesity	1.661	0.0412 sig
Gravidity	1.230	0.426 ns
Parity	1.140	0.238 ns
Lower gestational age at infection	2.542	0.007 sig
Previous cesarean section	1.031	0.483 ns
WBCs count	1.028	0.422 ns
NLR	1.174	0.222 ns
Severe disease form	3.825	0.001 sig

ns: not significant, sig: significant, WBCs: white blood cells , NLR: neutrophil to lymphocyte ratio, OR: odds ratio

4. DISCUSSION

COVID-19 is a pathology of great epidemiological importance in the current context due to the rapid spread of the virus and the fact that outbreaks can grow at an exponential rate ; added to the presence of serious complications that increase morbidity and mortality (18,19). The global spread of the virus has overwhelmed health systems and caused widespread social and economic disruption(20).Currently, in relation to the effect of this pandemic on pregnancy, there are more questions than certainties about the real impact of COVID-19 on pregnant women. Studies are updated and often contradict each other(21,22). There is no evidence to suggest that pregnant women with COVID-19 have higher morbidity than affected non-pregnant women. However, a sufficient number of pregnant women have not yet been studied to allow appropriate inferences to be made. It is known that SARS OR MERS infection significantly increases the number of maternal deaths, but this does not seem to be true in the case of COVID-19, but it does seem to increase the rate of premature birth, preeclampsia, caesarean section and perinatal death. However, there is still not enough information to confirm that there is no vertical infection in these pregnant women (23–25)

In the present study, most of the patients aged between 21 and 35 years and almost one third of each group were nulliparous. These data are consistent with other reports such as Saenz et al (26) and Chinn et al. (27).

In the laboratory tests performed, leukocytosis, higher neutrophil to lymphocyte ratio was reported in COVID-19 cases, which differs from the study by Yan et al.(28) carried out retrospectively in 25 Chinese hospitals in 116 obstetric patients, where they obtained a lower leukocyte value of 7900/ml; This is probably due to the fact that in our study we present 82 COVID-19 patients in labor, which implies an increase in physiological leukocytes, In turn, in the retrospective study by Qiancheng et al., they evaluated pregnant women and detected leukocytosis in (35.7%) of pregnant patients with COVID-19 which is close to the 42.7% in our study(29).

We also observed an elevation of C-Reactive protein , in almost 67.1% of patients, Yan, et al. found an elevation of this parameter in 44% of the patients, it is well identified that a systemic inflammatory condition would translate into an elevation of this parameter (28).

D-dimer was found elevated in 52.4%, however, majority of studies reported elevated D-dimer among COVID-19 patients; in a study conducted by Qiancheng et al. (29). 92.3% of

pregnant patients had elevated D-dimer. This can be explained because COVID-19 is associated with microthrombosis, therefore, the value of D-dimer is relevant and is used as criteria of severity(30).

We documented elevated serum ferritin in 35.4% of cases, Chen et al (31) analyzed the clinical characteristics of 99 patients, in whom (63%) presented serum ferritin above normal levels, another study conducted by Erol et al. (32) found higher S. ferritin in pregnant women with COVID-19 compared to healthy controls, S. ferritin, is known as one of the measures of inflammatory process and its severity and also may reflect the potential impact of impaired iron metabolism in patients with COVID-19 (32).

In our study, 15.9% of patients had severe COVID-19, which is higher than the rate reported by Lokken, et al. (33) who found that 9.2% of the patients had severe disease; However, like them, our patients also presented major complications such as multiple organ failure, septic shock, severe respiratory failure requiring invasive ventilation, and renal failure that lead to death of 2 cases giving a mortality rate of 2.4% a higher value than that found by Lokken, et al. (33) who had 1.3%; However, we agree on the pathophysiology of the cause of death, since the first patient with maternal death was referred in a puerperal state from another institution where she had managed for severe preeclampsia and it is believed that the cause of death due to endothelial dysfunction associated with the hypertensive disorder of pregnancy and that generated by COVID. As Mendoza et al postulate, indicating that severe COVID can simulate processes similar to severe preeclampsia syndrome and HELLP syndrome (34).

It has not been shown that SARS-CoV-2 infection during pregnancy is associated with an increased risk of miscarriage and spontaneous preterm birth, however, some published series describe a higher incidence of complications during pregnancy or childbirth in women. affected by COVID. Schwartz et al. (35) in a series of 38 pregnancies, describe gestational diabetes, preeclampsia, uterine rupture, gestational hypertension and hypothyroidism and in relation to childbirth, the fetus or the newborn: preterm births, fetal distress, premature rupture of membranes, alterations of the umbilical cord, placenta previa, chorioamnionitis, oligo and polyhydramnios and meconium amniotic fluid.

Although the mode of delivery is decided by the usual obstetric indications and the general condition of the patient, it is necessary to comment that such a decision should not be strictly influenced by the presence of the disease (36,37) the termination of pregnancies has

been protocolized by the fastest way, including cesarean section, but mainly based on obstetric indications, in order to reduce the time of exposure of health personnel and to the aerosols that are produced in the second stage of labor. On the other hand, many patients were referred to our hospital, for termination of pregnancy, due to a history of previous cesarean sections, which contributed to the high percentages of cesarean sections (63%). Similarly higher cesarean rates reported by Zhang et al. from China (38).

Adverse neonata outcomes reported in our study were almost close to that reported in previous studies with some differences in the reported rates of these complications, However, Zhu et al. (11) found a high rate, 60%, of preterm infants, , and this is probably due to the fact that at the beginning of the pandemic, when COVID-19 was diagnosed, it was decided to terminate gestation quickly.

Regarding the Apgar assessment, 14.6% newborns had < 7 at 5 minutes, with a diagnosis of perinatal asphyxia. Chen et al. (39) and Yu et al. (2) reported that all the newborns studied had Apgar scores at 1 minute and 5 minutes ≥7 in both studies. On the other hand, Di Mascio et al.(25) found that the rate of Apgar score <7 at 5 minutes was 4.5%, and no cases of neonatal asphyxia were reported.

It was found that 17.1% of the neonates were admitted to the NICU, with a diagnosis of sepsis, transient tachypnea of the newborn, hyaline membrane disease and other causes; 3 neonates with a 3.7% mortality rate. Zhu et al. (11) studied 10 hospitalized neonates, 10%died. Di Mascio et al. (25) in a systematic review, report a perinatal death rate of 7% including 1 stillbirth (2.4%) and one neonatal death (2.4%).

However, the exact effect of COVID-19 on maternal and neonatal pregnancy outcomes still under debate and further studies are needed for more clarification

The main limitation of the study is related to the retrospective nature of the research, which does not allow the risk of this disease in pregnant women to be measured in its acute stage, as could be done in a cohort study. Due to the characteristics of the disease and its treatment, it is not feasible to carry out this type of study. It was not possible to analyze other maternal complications due to the absence of serious positive cases, which are usually sent to more complex care centers.

5. CONCLUSION

Infection with COVID-19 had a significant effect on pregnancy outcome, infected women were more likely to have higher incidence rates of adverse perinatal outcomes in both mothers and the newborns. Also higher odds of complications associated with severe disease form Findings of our study came in line with previous studies in other countries, however, more medical care and support should be provided to pregnant women infected with COVID-19, particularly severe cases. Further studies with larger sample size are still needed for good understanding of the effect of virus on pregnancy outcomes.

Ethical Issues: All ethical issues were approved by the authors. Verbal and signed informed consents were obtained from all patients who included in the study during their first visit.

Conflict of interest: None

Source of funding: Authors declared no funding agency, or organization

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