Inflammatory Cytokines—The Link between Coronavirus Disease and Abortion: A Case-Control Study

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Abstract

Background: Coronavirus disease (COVID-19) infection and the risk of abortion have become a major concern for pregnant women worldwide. Whereas research studies have not yet determined the exact risk of abortion due to COVID-19 infection, the virus could increase the risk of pregnancy complications through inflammatory cytokines and immune response. **Objective:** The study highlights prognostic markers for pregnancy complications during COVID-19 infections by testing interleukin-6 (IL-6), interleukin-18 (IL-18), tumor necrosis factors-α (TNF-α), and interferon-γ (INF-γ) in the serum of pregnant women with and without COVID-19. **Materials and Methods:** A case-control study consists of 100 cases; included are 50 COVID-19 pregnant women matched with 50 non-COVID-19 pregnant women, with both groups free from any abortion risk factors. The study measured serum IL-6, IL-18, TNF-α and INF-γ tests to predict cases with severe infection and those at high risk for fetal loss. **Results:** The statistical analysis showed a significant relationship between elevated immunological markers levels and the severity of COVID-19 and pregnancy complication *P* value (0.001, 0.005, 0.001, and 0.001 for IL-6, IL-18, TNF-α, and INF-γ, respectively). Furthermore, the odd ratio explains that elevated immunological markers increased the risk of baby loss; through COVID-19 infection. In addition, receiver operating characteristic curve analysis verified these accuracies; the excellent test referred to IL-6, followed by IL-18 and INF-γ very good tests, then TNF-α as a medium test to predict the risk of pregnancy complication. **Conclusion:** These results concluded that monitoring these immunological markers' levels could help predict COVID-19 infection in the severe stage and the risk of pregnancy complications in COVID-19-positive women.

Keywords: Coronavirus, IL-18, interferon-gamma, interleukin-6, pregnancy complication, tumor necrosis factors α

Introduction

Coronavirus disease (COVID-19) is a new strain of the coronavirus family described in December 2019 in Wuhan, China, and fast spread worldwide, and it can be fatal and cause severe illness.[1] COVID-19 first case was reported in Iraq on February 24, 2020. After that, the COVID-19 pandemic spread fast through Iraq, and new cases are reported every hour daily.[2,3]

Pregnancy is a complex and transformative physiological process involving numerous changes in a natural woman's body to protect the fetus; one critical aspect of these changes is the immune system's response, specifically the role of proinflammatory cytokines.[4-7] Pregnancy and immune system cytokines interplay in a delicate balance essential for maintaining maternal and fetal health.[8-10] During pregnancy, the mother's immune system undergoes significant modifications to tolerate the fetus, which is half-allogeneic.[11-13] However, these adaptations may also affect the susceptibility of pregnant women to viral infections. As a result, the pregnant immune system is more vulnerable to viral infections than the non-pregnant immune system and can have severe consequences for both the mother and the fetus.[14-17]

The COVID-19 pandemic has impacted almost every aspect of human life, including reproductive health.

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One area of concern is the potential risk of pregnancy complications, including abortion, associated with COVID-19 infection.[18]

The number of COVID-19 pregnant women admitted to intensive care units and hospitals are more than non-pregnant women infected with COVID-19, according to the American Centers for Disease Control. While both groups have the same mortality rate addition, another study explains the role COVID-19 in coagulation disorders that may negatively affect pregnancies.[5,17]

The information about the effect of COVID-19 on the pregnancy period, its manifestations, and outcomes remain limited, so the current research focused on exploring whether COVID-19 infection increases the risk of pregnancy complications during pregnancy through the immune system responds to viral infections. Furthermore, discuss the possible implications of these findings for maternal and fetal health. So the present study aims to highlight prognostic markers for pregnancy complications during COVID-19 infections by examining four cytokines, interleukin-6 (IL-6), interferon-γ (INF-γ), interleukin-18 (IL-18), and tumor necrosis factors-α (TNF-α) in the serum of pregnant women with COVID-19 and free from it.

Materials and Methods

Study design

A prospective case-control study was conducted in Al-Yarmouk Teaching Hospital, Baghdad, Iraq, between May 2021 and March 2022. The study included 100 pregnant women divided into two groups. Where first group comprised 50 cases admitted to the Department of Obstetrics and Gynecology, all confirmed to have COVID-19 by reverse transcription polymerase chain reaction for nasal and throat swabs compared to 50 pregnant women free from COVID-19 as a control. The study excluded all pregnant women with other diseases and defined risk factors. Moreover, hospitalized COVID-19 pregnant women are cared by a team of specialists in perinatologists, obstetricians, infectious diseases, and neonatologists.

The routine hematological markers such as ferritin, D-dimer, CRP, ESR, HDL, RBC, hemoglobin, WBC, and albumin were done for all cases. In addition, immunological study markers (IL-6, IL-18, TNF-α, and INF-γ) were measured by using an enzyme-linked immunosorbent assay (ELISA) test. The severity of the disease has been determined according to COVID-19 criteria.[9,10] Human ELISA Kit was used for IL-6 (ab178013); TNF-α (ab181421); IL-18 (ab215539), and INF-γ (ab174443) abcaml USA.

Ethical approval

The ethical authority protocol was approved by the Iraq Ministry of Health and the institutional ethics committee (n5-2021 on February 14, 2021).

Statistical analysis

The study used a one-way analysis of variance for multiple comparisons between variables among study groups, the Spearman test, to assess the correlation between pregnancy complications and inflammatory variables during COVID-19 infection. Using an odd ratio, they measured the risk of pregnancy complications with high levels of inflammatory cytokines in pregnant women with COVID-19. Also, the sensitivity and specificity of the test were measured by receiver operating characteristic curve (ROC). Analyses were completed using SPSS version 23 (Statistical Package for Social Sciences, IBM SPSS Statistics 23.0, Chicago, IL). Additionally, P value significant ≥ 0.005.

Results

Demographic and clinical characteristics in pregnant patients with and without COVID-19

The current study demonstrated no significant effects of age and body mass index (BMI) in the cases/control. However, simultaneously, there was a rise in the level of hematological markers in the COVID-19 pregnant women compared with control.

Also, the tables show that pregnant women with COVID-19 developed significant pregnant complications among 50 pregnant women 30 of them completed with normal pregnancy,10 of them developed gestational diabetes and hypertension, 3 miscarriage, 4 pre-eclampsia, and 3 preterm delivery.

Hematological and immunological markers

The results also show that there is a significant increase in hematological markers in infected women compared with non-infected pregnant women also; Table 1 explains that there are significant complications during pregnancy in COVID-19 pregnant women also; the same table shows there is a significant increase in mean with the severity of COVID-19 P value (0.001, 0.005, 0.001, 0.001 for IL-6, IL-18, TNF-α, and INFγ, respectively).

Table 3 shows R in Spearman test levels of immunological markers and pregnancy complications matched with the severity of disease, where R in pregnant complication 0.567, 0.405, 0.337, 0.609 $P < 0.001$, 0.001, 0.13, and 0.001 whereas R with COVID-19 severity 0.631, 0.783, 0.462, and 0.568 P value 0.001, 0.001, 0.04, and 0.001 for IL-6, IL-8, TNF-α, and INF-γ, respectively.

The study has revealed that the levels of IL-6, IL-18, TNF-α, and INF-γ are elevated with the severity of COVID-19 and the risk of losing a baby during pregnancy. Our analysis indicated that the expression of these immunological proteins could help control the infection's severity and be used as a prognostic marker. ADditionally, our Odds Ratio analysis showed in Table 2 that risk increased with high

Table 1: The means of a demographic, hematological and immunological markers pregnancy among pregnant women with and without COVID-19

Variables	Status	*N*	Mean	Std. deviation	Std. error	95% confidence interval for mean		*P* value
						Lower bound	Upper bound	
BMI	G1	50	0.2116	0.2423	0.6341	0.1121	0.5127	0.120
	G2	50	0.1871	0.3947	0.4233	0.2131	0.6583	
Ferritin (ng/mL)	G1	50	638.13	124.852	32.237	568.99	707.27	0.005
	G2	50	267.09	107.957	19.084	228.17	306.02	
D-dimer (mg/L)	G1	50	1.3333	0.48795	0.12599	1.0631	1.6036	0.014
	G2	50	0.5388	0.29846	0.05276	0.4312	0.6464	
CRP (mg/dL)	G1	50	19.07	3.127	0.808	17.33	20.80	0.003
	G2	50	11.06	2.355	0.416	10.21	11.91	
LDH (mg/L)	G1	50	433.00	40.334	10.414	410.66	455.34	0.001
	G2	50	260.16	62.519	11.052	237.62	282.70	
Lymphocyte	G1	50	0.4073	0.29789	0.07692	0.2423	0.5722	0.081
	G2	50	0.4739	0.29704	0.05251	0.3818	0.5959	
RBS (mg/dL)	G1	50	278.60	12.040	3.109	271.93	285.27	0.005
	G2	50	113.47	32.822	5.802	101.64	125.30	
ESR	G1	50	37.73	4.148	1.071	35.44	40.03	0.005
	G2	50	19.53	6.416	1.134	17.22	21.84	
Hemoglobine	G1	50	1.5957	0.5537	0.18311	2.1395	2.9374	0.002
	G2	50	2.5385	0.66023	0.09496	1.0421	1.4285	
Albumin (mg/dL)	G1	50	2.13	0.834	0.215	1.67	2.60	0.01
	G2	50	4.66	1.208	0.214	4.22	5.09	
IL-18 (pg/mL)	G1	50	562.7	151.4	21.42	519.7	605.8	0.001
	G2	50	70	35.68	5.045	59.86	80.14	
TNF (pg/mL)	G1	50	35.94	15.90	2.249	40.42	59.46	0.005
	G2	50	23.02	17.11	2.419	18.16	27.88	
INF-γ (pg/ml)	G1	50	464.4	144.2	20.39	423.4	505.4	0.0001
	G2	50	96.08	38.05	5.382	85.26	106.9	
IL-16 (pg/mL)	G1	50	56.94	13.41	1.897	53.13	60.75	0.0001
	G2	50	16.96	6.590	0.9320	15.09	18.83	
Pregnant complication type among COVID-19 infections (50)								
Normal		30	1.5946	0.96399	0.1102	1.3875	1.8267	0.001
Miscarriage		3	3.8	0.44721	0.2102	3.333	4	
Pre-eclampsia		4	3.75	0.46291	0.1699	3.3756	4	
Pretern delivery		3	3	1	0.5419	2	4	
Gestational diabetes mellitus		5	3.625	0.51755	0.1819	3.25	4	
Gestational hypertension		5	3.5	0.70711	0.3815	3	4	

G1: Pregnant women with COVID 19, G2: Normal pregnant women without any risk factors, *N*: number, *P*-value < 0.05; sig: significant, CRP: C-reactive protein, RBC: red blood cell, ESR: erythrocyte sedimentation rate, LDH: lactate dehydrogenase

Table 2: Odd ratio of the immunological marker as the risk for pregnancy complications among study groups

Immunological marker	Relative risk ratio	95% CI	*P* value
IL-18 (pg/mL)	3.88	1.56-9.65	0.001
IL-6 (pg/mL)	4.33	1.78-10.53	0.001
TNF-α (pg/mL)	0.95	0.39-2.13	0.13
INF-γ (pg/mL)	1.26	0.23-6.84	0.001

levels of IL-6 followed by IL-18, then INF-γ, whereas low risk with TNF-α (odd ratio: 3.88, 4.33, 1.26, and 0.95 for IL-18, IL-6, INF-γ, and TNF-α, respectively)

The ROC curve [Table 4; Figure 1] was used to confirm the validity of these tests. The area under the curve explains that IL-6 and INF-γ used as an excellent test for severe cases of COVID-19 (AUC: 0.975 and 0.946 for IL-6 and INF-γ), IL-18 was a good test (AUC: 0.894), and fair test used for TNF-α (AUC: 0.720).

In case of evaluating the risk of loss of baby and pregnancy complications, the excellent test referred to IL-6, followed by IL-18 and INF-γ is a good test, then TNF-α could be a poor test (AUC: 0.915, 0.830, 0.677, and 0.851 for IL-6, IL-18, TNF-α, and INF-γ respectively).

Discussion

The first COVID-19-infected cases were reported in Wuhan, Hubei province, China, and then it rapidly spread worldwide.[8,19] During pregnancy, the immune system modulation to protect the fetus leads to immunological and physiological changes that may increase susceptibility to infection.[14-18]

The statistical results show that hematological markers significantly correlated with the severity of infection during pregnancy. In addition, these results correlated with Zaigham and Andersson.[16] The present study shows that during COVID-19 severe course, women suffer from a complication that leads to the loss baby. Furthermore, this study correlated with the study of Wastnedge *et al.* (2021) and study of Tanacan *et al.* (2021), who discuss the risk of COVID-19 on fetus survival because hematological markers cannot explain the exact risk of fetus loss.[19,20] Therefore, we need a new immunological marker that may help predict pregnancy complications during COVID-19 infection that may affect the fetus's life.[19,21]

The present study showed that IL-6, IL-18, TNF-α, and INF-γ significantly differed in levels between study groups which increased in COVID-19 and the risk of severe progress. In addition, the high level of IL-6, IL-18, TNF-α, and INF-γ correlates positively with severe cases, which concur with the study of Duan *et al.*[20,22] and Ghazavi A *et al.*,[22] who explained that cytokines can increase the

Table 3: Spearman test explains the correlation of IL-18, IL-6, TNF-α and INF-γ gamma with COVID-19 severity and pregnancy complications among pregnant women with COVID-19

Immunological marker	Pregnancy complications		COVID 19 severity	
	R-value	*P* value	*R*-value	*P* value
IL-18 (pg/mL)	0.567	0.001	0.631	0.001
IL-6 (pg/mL)	0.405	0.001	0.783	0.001
TNF-α (pg/mL)	0.337	0.13	0.462	0.04
INF-γ (pg/mL)	0.609	0.001	0.568	0.001

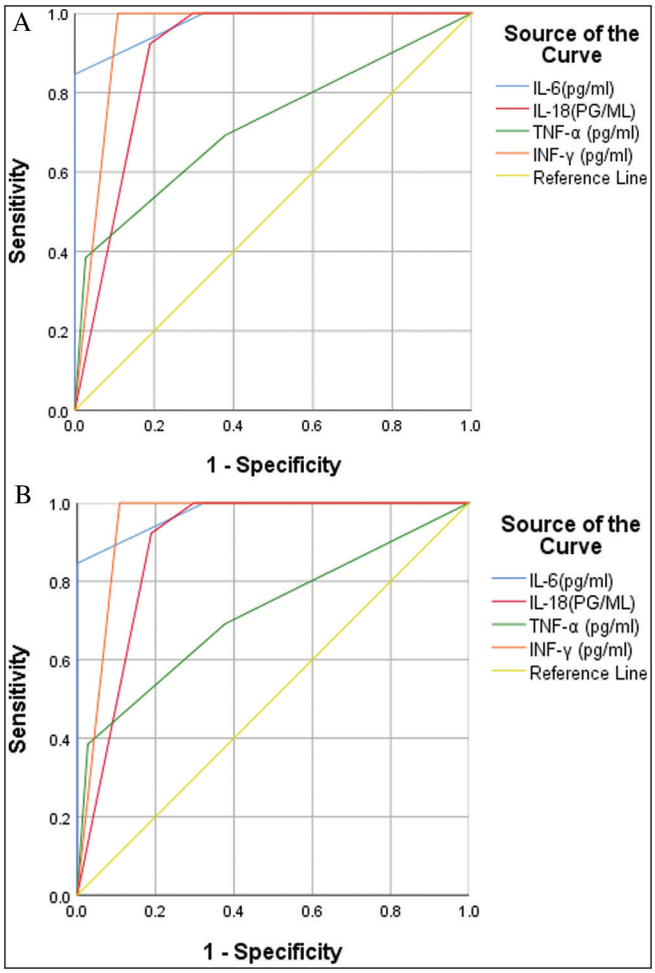

Figure 1: IL-6, IL-18, TNF-α, and INF-γ receiver operating characteristic curve (ROC) to predict the balance between sensitivity and specificity among study groups; (A) Immunological marker to predict pregnant complications. (B) Immunological markers and COVID-19 severity

Table 4: The immunological markers area under the ROC curve to prognosticate cases with a high risk of loss of baby and severe COVID-19 infections

Four immunological markers	AUC	Std. error	*P* value	Asymptotic 95% confidence interval	
				Lower bound	Upper bound
Area under the curve for immunological markers to predict COVID 19					
IL-6 (pg/mL)	0.975	0.021	0.000	0.933	1.000
IL-18 (pg/mL)	0.894	0.044	0.000	0.807	0.981
TNF-α (pg/mL)	0.720	0.091	0.019	0.541	0.900
INF-γ (pg/mL)	0.946	0.032	0.000	0.884	1.000
Area under the curve for immunological markers to predict pregnancy complications					
IL-6 (pg/mL)	0.915	0.045	0.017	0.826	1.000
IL-18 (pg/mL)	0.830	0.073	0.057	0.686	0.973
TNF-α (pg/mL)	0.677	0.180	0.307	0.325	1.000
INF-γ (pg/mL)	0.851	0.066	0.043	0.721	0.981

AUC: Area under the curve

True area significant $P \leq 0.5$

risk of COVID-19 severe progression and developing of cytokine storm. Also, Mortaz *et al*.,[23] concluded that high levels of TNF-α correlated with severe cases and mortality rates.

The current results spotlight the effects of four immunological markers on pregnancy complications and demonstrate that IL-6, IL-18, TNF-α, and INF-γ positively correlate with pregnancy complications. Furthermore, the odd ratio of immunological markers explains the risk in various levels in the top IL-6 with a high-risk ratio followed by IL-18, then INF-γ and finally, TNF-α with the lowest risk.

The results agree with Tanacan *et al*. study,[19] which showed that IL-6 and INF-γ significantly correlated with the severity of the disease and the high chance of losing the baby.

Moreover, Ghazavi *et al*.[22] showed that INF-γ induces and mediates the inflammatory response in severe COVID-19 cases. The study by Duan *et al*.[20] concluded that IL-6 and IL-18 correlate with pregnancy complications during COVID-19.

Also, a study by Soheilyfar *et al*.,[24] concluded that IL-18 might be associated with the recurrence of pregnancy loss and a study by Akinori *et al*.,[25] who studied the link between high levels of IL-18 and pregnancy complications and study Sanja *et al*.[26] who showed a positive correlation between loss baby and high levels of IL-18.

IL-16 as an inflammatory marker expressed increased with COVID-19 during pregnancy; one of the essential factors that may affect pregnancy is cytokine; it is a mediator that functions as a regulation of immune response, and there are three forms pre, proinflammatory, anti-inflammatory, balanced between proinflammatory and anti-inflammatory helps to protect the fetus from rejections.[27-29]

IL-6 plays a role in the regulation of embryo implantations and growth of the placenta, which helps to immune adaptation needed for tolerance. Also, these interleukin elevated infection and tissue damage to stimulate acute inflammation and hematopoiesis.[21,23]

The complication can occur during pregnancy in severe cases resulting from COVID-19 infection, activating INF-γ as an antiviral. Production of cytokines can lead to the over-activation of immune cells to cause a storm of cytokines that may affect fetus survival which is correlated with the pathogenesis of pre-eclampsia by affecting endothelial function and causing maternal inflammation.[24,28] Additionally, IL-18 can induce the secretion of INF-γ through binding with receptors on endothelial cells leading to activating T-helper cell type 1, which promotes an inflammatory process that may increase the secretion of IL-6.[27-30]

Conclusion

These results concluded that monitoring these immunological markers' levels could help predict COVID-19 infection in the severe stage and the risk of pregnancy complications in COVID-19 positive women.

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Conflicts of interest

There are no conflicts of interest.

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