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Short Communication

Comparison of vascular cell adhesion molecule 1 (VCAM-1) during pregnancy, after placental detachment and during puerperium between normal and pregnancy with COVID-19

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Abstract

Pregnant women have a number of physiological changes that lower the immune responses to avoid embryonic rejection, which increases the risk of problems after contracting coronavirus disease 2019 (COVID-19). Multiple inflammatory cytokines are dysregulated in this process and expressed inappropriately during systemic inflammatory responses associated with COVID-19. The aim of the study was to compare the levels of vascular cell adhesion molecule 1 (VCAM-1), a marker of endothelial damage in pregnancies with and without COVID-19. A cohort prospective study was conducted at H. Adam Malik General Hospital and the Universitas Sumatera Utara Hospital, Indonesia. Pregnant women without COVID-19 and pregnant women with moderate and severe degrees of COVID-19 were recruited. The level of VCAM-1 was measured at three different time points (during pregnancy, within an hour of placental detachment, and 24 hours postpartum). The ANOVA and Student t-test were used to compare the VCAM-1 levels among different time points and between groups, respectively. The mean VCAM-1 levels at the hospital admission, one hour of placental detachment and 24 hours postpartum in non-COVID-19 and COVID-19 pregnancies were 591.29 vs 1176.27 pg/mL; 558.2 vs 1136.2 pg/mL; and 508.59 vs 985.2 pg/mL, respectively. There was a significant different in VCAM-1 levels in normal pregnancy at the time of hospital admission, one hour after detachment of the placenta and 24 hours postpartum (p=0.04). The mean VCAM-1 levels in pregnant women with COVID-19 also had significant differences between three time points (p=0.033). The levels of VCAM-1 were statically higher among pregnancy in the COVID-19 group compared to the non-COVID-19 group during hospital admission (p=0.023), one hour after placenta detachment (p=0.040) and 24 hours postpartum (p=0.043). The results suggested the usefulness of identifying the VCAM-1 level as a marker of endothelial dysfunction in pregnancy with COVID-19.

Keywords: COVID-19, pregnancy, endothelial dysfunction, VCAM-1, vascular cell adhesion protein 1

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Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is one of the biggest threats to society's health system recorded in

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human history [1]. Due to worries about how COVID-19 will affect pregnant women during and after pregnancy as well as their unborn children, pregnant women are classified as a high-risk population [2]. Since COVID-19 is similar to severe acute respiratory syndrome (SARS), the probability of vertical transmission from mother to fetus in COVID-19 may be as low as in SARS [2]. However, pregnant women undergo a number of physiological changes that lower their immune responses which increases the risk of severe problems after contracting COVID-19 [3].

Multiple inflammatory cytokines are dysregulated and expressed inappropriately during a systemic inflammatory response in COVID-19 [4]. The recruitment and activation of inflammatory cells require the expression of several classes of inflammatory mediators, including chemokines, cytokines such as interleukin (IL)-18, IL-6, and IL-1, vascular cell adhesion molecule 1 (VCAM-1), intercellular adhesion molecule 1 (ICAM-1), and adhesion molecules such as cell-to-cell adhesion molecule 1 [5]. Pro- and anti-inflammatory factors are released as a result of endothelium injury, such as pro-inflammatory factor VCAM-1 [6]. COVID-19 patients are expected to have higher levels of endothelial cell adhesion biomarkers controls. Therefore, the aim of this study was to determine the VCAM-1 levels in pregnant women with COVID-19 and to compare with the pregnancies without COVID-19. In addition, the study also aimed to compare the levels of VCAM-1 between those two groups after placental detachment and during the puerperium phase.

Methods

Study design and setting

A cohort prospective study was conducted at H. Adam Malik General Hospital and the Universitas Sumatera Utara Hospital, Medan, Indonesia. The study was conducted in collaboration with Prodia Laboratory. The sample was collected starting March 1, 2022, until the targeted sample size was completed. The pregnant women were followed until postpartum.

Patients

Pregnant women with no evidence of COVID-19 and pregnant women with confirmed COVID-19 were recruited in this study. The inclusion criteria were pregnant women of any age with a gestational age of ≥34 weeks regardless of parity were considered eligible for the control group. Pregnant women with moderate and severe degrees of COVID-19 at all ages with a gestational age of ≥34 weeks regardless of parity were set as inclusion criteria of the case group. All pregnant women with gemelli, diabetes mellitus, hypertension, hyperlipidemia, any blood disorder and immune disorder were excluded.

Data collection

Demographic and clinical data were collected from all patients during pregnancy (≥ 34 weeks) at hospital admission. The blood sample was collected at hospital admission, one hour post placenta detachment, and 24 hours postpartum.

End point

The end point in this study was the level of VCAM-1, a biomarker of endothelial damage in pregnancy with and without COVID-19. Serum VCAM-1 levels in both groups were measured on three separate occasions: during pregnancy (≥34 weeks) at hospital admission, one hour after placental detachment, and 24 hours postpartum. The immunoenzymemetric method was used to determine the level of VCAM-1 using VCAM1 Protein, Human, Recombinant (His Tag) kit (SinoBiological, Beijing, China) following the manufacturer protocol.

Statistical analysis

The changes in VCAM-1 level data in three separate times were compared using the analysis of variance (ANOVA) test. Student t-test was conducted to compare VCAM-1 levels between COVID-19 and non-COVID-19 groups within each time point. The collected data were analyzed using the statistical software SPSS 26.0 (IBM, New York, USA).

Results

Characteristics of patients

There were 25 normal pregnancies and 18 pregnant women with COVID-19 recruited in this study. The characteristics of pregnant women with and without COVID-19 are presented in **Table 1**. The mean age of pregnancies with COVID-19 was 29.16 years while 28.28 years for normal pregnancies. The average gravida and parity in normal pregnancies were 2 and 1, respectively, while the mean gravida and parity for the COVID-19 group were 3 and 2, respectively.

The gestational age at birth in healthy and COVID-19 groups was 39 weeks and 38 weeks, respectively. Out of the total pregnancies with COVID-19, 16 of them had cesarean section while 15 women with non-COVID-19 had caesarean section. Student t-test and Fisher's exact test indicated the was no significant difference between pregnancy women with and without COVID-19 for all characteristics, all had $p>0.05$ (**Table 1**).

Table 1. Characteristics of patients of normal pregnancies and pregnancies with COVID-19

Characteristics	Normal pregnancy (n=25)	Pregnancy with COVID-19 (n=18)	*p*-value
Age, mean±SD	28.28±4.097	29.16±2.854	1.000
Gravida, mean (range)	2 (1–3)	3 (2–4)	0.975
Parity, mean (range)	1 (1–2)	2 (2–3)	0.975
Gestational age, mean (range)	39 (39–40)	38 (36–38)	1.000
Delivery method			0.625
Cesarean section, n (%)	16 (64%)	15 (83.3%)	
Spontaneous vaginal delivery, n (%)	9 (36%)	3 (16.6%)	

Comparison of VCAM-1 level

The comparison of VCAM-1 levels between COVID and non-COVID groups is presented in **Table 2**. The mean VCAM-1 levels in normal pregnancies at the time of hospital admission, one hour after the separation of the placenta and 24 hours postpartum were 591.29, 558.2 and 508.59 pg/mL, respectively (**Table 2**). In pregnancies with COVID-19, the mean VCAM-1 level at the time of admission, one hour after placenta detachment, and 24 hours postpartum were 1176.27, 1136.2 and 985.2 pg/mL, respectively. The VCAM-1 levels in healthy pregnancies were significantly different between admission time, one hour after placenta detachment, and 24 hours following delivery ($p=0.04$) of which there was a decrease trend. The mean VCAM-1 levels were also significantly different among three time points ($p=0.033$) of which a decreasing trend was also observed (**Table 2**). Student t-test confirmed that the levels of VCAM-1 were statically higher among pregnancy with COVID-19 patients compared to the non-COVID-19 group for all three time points: during at hospital admission ($p=0.023$), one hour after placenta detachment ($p=0.040$) and 24 hours postpartum ($p=0.043$) (**Table 2**).

Table 2. Comparison of VCAM-1 levels at hospital admission, one hour after placenta detachment and 24-hours postpartum in pregnant women with COVID-19 and non-COVID-19

Group	VCAM-1 level (pg/mL)			*p*-value [a]
	At hospital admission	One hour post placenta detachment	24 hours postpartum	
Pregnancy without COVID-19 (n=25)	591.29±93.69	558.2±88.3	508.59±72.0	0.040*
Pregnancy with COVID-19 (n=18)	1176.27±256.7	1136.2±246.5	985.2±155.1	0.033*
p-value [b]	0.023	0.040	0.043	

[a] ANOVA test comparing VCAM-1 levels among three different time points within non-COVID-19 or COVID-19 groups

[b] Student t-test comparing VCAM-1 levels between non-COVID-19 and COVID-19 groups at one time point

Discussion

In this study, there were significant differences in VCAM-1 levels between hospital admission, one hour post placenta detachment and 24 hours postpartum in normal pregnancies ($p=0.040$).

VCAM-1 levels in pregnancies with COVID-19 at hospital admission, one hour post placenta detachment and 24 hours postpartum were also significantly different (p=0.033). Similar to our study, a retrospective study of 39 COVID-19 patients and 32 control subjects in China found that the levels of VCAM-1 were increased in the acute phase of illness and reduced in the convalescent phase [5]. The increased expression of molecular adhesions in endothelial cells is related to the COVID-19 severity and may have an impact on coagulation dysfunction [5]. Another study investigated the function of coagulation, endothelial damage, angiogenesis biomarkers, and innate immune response in vitro in endothelial cells exposed to preeclampsia and COVID-19-affected pregnant women's serum [7]. The results indicated endothelial damages in both severe COVID-19 and preeclampsia [7]. Studies indicate that COVID-19 is associated with prothrombotic changes, elevated laboratory markers of coagulopathy, and increased risk of thrombosis suggesting that microvascular thrombosis is likely a major pathophysiologic event in COVID-19 [8,9]. Relationship between endothelial damage and the extent of immune-inflammatory responses highlights that inflammatory-driven processes are likely primary drivers of endothelial damage leading to microvascular thrombosis and organ failure in COVID-19 [10,11].

The pathophysiology of multiorgan dysfunction in patients with COVID-19 is still poorly understood. Patients with COVID-19 seem to have a specific respiratory failure pattern characterized by initial good compliance despite severe hypoxemia [12]. This discrepancy could be linked to ventilation-perfusion mismatch and the loss of hypoxic pulmonary vasoconstriction because of endothelial damage with subsequent activation of coagulation and widespread microvascular thrombi formation in the lungs and other organs [13].

In a large national cohort of women hospitalized for childbirth in the United States, the absolute rates of death and adverse events among individuals identified with COVID-19 were low [14]. Nevertheless, in-hospital mortality, venous thromboembolism, and preeclampsia were significantly greater in women with COVID-19 than in those without COVID-19, despite the slight absolute risk differences [14]. The proportion of cesarean births and iatrogenic preterm birth is also high in pregnancy with COVID-19 which provides clear evidence of the indirect impact of COVID-19 on maternity care in a high-income setting [15]. A cohort study in Iran showed that pregnancy with COVID-19 had a higher cesarean delivery rate, higher preeclampsia event and greater rate of premature labor [16].

A study provided clear evidence to support the meaningful temporal relationship between COVID-19 and preeclampsia of which the median time interval between SARS-CoV-2 infection diagnosis and preeclampsia diagnosis was 3.79 weeks [17]. SARS-CoV-2 infection diagnosed before 32 weeks of gestation only was associated with a higher risk of developing preeclampsia [17]. SARS-CoV-2 infection closer to term was not associated with a significant increase in the risk for preeclampsia because the time remaining to develop the clinical disorder was limited [17,18]. Nevertheless, a meta-analysis showed that SARS-CoV-2 infection diagnosed at any time during pregnancy was significantly associated with an increased risk for preeclampsia [19]. Although similar to the in vitro endothelial dysfunction model, preeclampsia and severe COVID-19 exhibit distinctive profiles of circulating biomarkers related to endothelial damage, coagulopathy, and angiogenic imbalance that could aid in the differential diagnosis of these entities [20].

Conclusion

Based on the data obtained by our research, the observed VCAM-1 levels were increased significantly during admission in pregnancy with COVID-19 than those without COVID-19 and dropped until 24 hours postpartum. In the 24-hour postpartum period, the VCAM-1 level in patients with COVID-19 was still noticeably higher than in patients without COVID-19. This result has confirmed the usefulness of identifying the VCAM-1 level as a marker for endothelial dysfunction in pregnancy with COVID-19. Further research is required to fully confirm the effectiveness of this biomarker with a larger population and more diverse characteristics of patients.

Ethics approval

This research was approved by the Health Research Ethics Committee of the Faculty of Medicine Universitas Sumatra Utara No 585/KEP/USU/2022 to conduct the study.

Competing interests

The authors declare that there is no conflict of interest.

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Underlying data

Derived data supporting the findings of this study are available from the corresponding author on request.

How to cite

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