ORIGINAL ARTICLE

The role of serum and placental vascular cell adhesion molecule-1 levels in placenta accreta

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ABSTRACT

Keywords: Vascular cell adhesion molecule-1 (VCAM-1), Serum, Invasion, Pregnancy, Placenta accreta.

Background: Vascular cell adhesion molecule-1 (VCAM-1) is one of the cell adhesion molecules which is expressed in endothelial cells. In pregnancy, VCAM-1 is involved in placentation by promotion of angiogenesis and trophoblastic invasion. Placenta accreta (PA) is a term that refers to abnormal adherence of the placenta to the uterine myometrium. The incidence of PA rises as the number of elective cesarean sections and pregnancies with placenta previa increases. Objectives: This study discusses the role of VCAM-1 in normal pregnancy, the pathogenesis of PA, and its predictive value for PA occurrence. Methods: Our longitudinal study included 62 pregnant women. Then they were divided into Group N: 31 pregnant women with normal placenta and Group P: 31 pregnant women with placenta accreta. Result: Serum VCAM-1 levels were higher in case of PA than those of normal pregnancy and it had a significant predictive value for PA with markedly high sensitivity and specificity. Conclusion: Detection of a high serum level of VCAM-1 in the 2nd trimester can predict the occurrence of PA in healthy women. Moreover, placental VCAM-1 may be implicated in the pathogenesis of PA through enhancing trophoblastic invasion.

INTRODUCTION

Vascular cell adhesion molecule-1 (VCAM-1) is one of the cell adhesion molecules, which is predominantly expressed in endothelial cells, tissue macrophages, and placental trophoblastic cells⁴. It is implicated in cell migration and adhesion thus its role is apparent in the pathogenesis of inflammation, and tumor metastasis⁵. The prime inducing factors for VCAM-1 production are the pro-inflammatory cytokines; tumor necrosing factor-α (TNF-α) and interleukin-1 (IL-1)⁶. In pregnancy, VCAM-1 is involved in placentation by promotion of angiogenesis⁷, and trophoblastic invasion⁸. Placenta accreta (PA) is an abnormal adherence of the placenta to the myometrium⁹. Decidual maldevelopment and excessive trophoblastic invasion are considered the main pathogenic mechanisms for PA¹⁰. It is considered a serious pregnancy-related complication that leads to catastrophic life-threatening intrapartum and postpartum hemorrhage¹¹. The ultrasonography with doppler examination are the gold standard tools for prediction and diagnosis of PA in the 3rd trimester¹². Our study aimed to highlight the potential predictive value of serum VCAM-1 levels in the 2nd trimester as a biochemical marker for the occurrence of PA.
SUBJECTS AND METHODS

From the 1st of October 2020 to the 1st of October 2021, a double-center longitudinal study was conducted by recruitment of 62 pregnant women with normal placenta and placenta accreta (PA) from Assiut Woman's Health Hospital and Aswan University Hospital, Egypt. Before recruitment, ethical approval was obtained from the ethics committee board of the Faculty of Medicine, Aswan University, approval NO: saw/4779/20, and Informed consent from all eligible participants was obtained after explaining the nature of the study. The sample size was assigned according to the study's primary outcome and its power (80%) using G-power software 3.1.9.7.

Eligible participants were enrolled according to the following inclusion criteria; gestational age between 24-36 weeks, Age between 20-40 years, Singleton pregnancy, high probability of PA by two-dimensional (2D) grayscale imaging, and color Doppler flow mapping. Meanwhile, women known to have metabolic syndrome, hypertension, bleeding disorders, cardiac, renal, endocrinial, autoimmune disease, and patients on anticoagulant therapy were excluded from the study. Then, the study participants were divided into two groups (n=31); Group N: pregnant women with normal placenta and Group P: pregnant women with placenta accreta. Both groups were further subdivided according to the time of blood sampling into NT2: normal pregnancy during 2nd trimester (24-28 W), NT3: normal pregnancy during 3rd trimester (32-36 W), PT2: PA during 2nd trimester (24-28 W), and PT3: PA during 3rd trimester (32-36 W).

Venous blood samples were collected from all participants in the 2nd and 3rd trimester, then centrifuged and the clear non-hemolyzed supernatant sera were analyzed for VCAM-1 level using corresponding ELISA kits purchased from Shanghai Korain Biotech Co., Ltd catalog No: E0203Hu according to the manufacturer's protocol.

At the time of delivery, placental tissue samples were collected in the form of two rectangular sections measuring (1.5 – 3.5 cm) in size from the decidual surface of the placenta of each participant. Half of the collected sections were fixed in 10% formalin for 24 h, then they were processed for histopathological examination, and the other half of placental sections were suspended in cold 1x Phosphate buffer saline (PBS), PH 7.4 and homogenized using the homogenizer, general laboratory homogenizer (GLH 650) Roto stator, then the homogenate was centrifuged, and the supernatant was analyzed for VCAM-1 levels using corresponding ELISA kits according to manufacturer’s protocol. The tissue supernatant results were recalculated and expressed per milligram (mg) protein of the tissue homogenate in each sample.

All statistical analyses were carried out with SPSS software version 20 (SPSS Inc., Chicago, IL, USA). Based upon the results of normality test, Analysis was performed between groups using Kruskal Wallis H followed by the Mann-Whitney U test. Linear regression analysis was carried out. Possible predictive value of VCAM-1 was assessed by ROC test. A value of P ≤ 0.05 was considered statistically significant. Results were expressed as means ± standard error of the mean (SEM).

RESULTS

Serum VCAM-1 levels exhibited significant higher levels in both; group PT2 and group PT3 in comparison to serum VCAM-1 levels of group NT2 and group NT3; respectively. Moreover, serum VCAM-1 levels of 3rd trimester groups; NT3 and PT3 had significant lower values in comparison to 2nd trimester groups; NT2 and PT2 as shown in table (1) and figure (1). Additively, in comparison to group N, placental tissue VCAM-1 level of group P showed significant higher values as shown in table (2).

Interestingly, in pregnant women with normal placenta versus pregnant women with placenta accreta, serum VCAM-1 level of the 2nd trimester groups was a significant predictor (P-value < 0.001) for the occurrence of placenta accreta, at cutoff value ≥ 79.89 ng/ml, with a sensitivity of
93.5% and a specificity of 96.8%, negative predictive value of 93.7, and positive predictor value of 96.7 as shown in table (3) and figure (2).

By hematoxylin and eosin, microscopic examination of placental sections of group N showed normally structured decidua separating basal plate of chorionic villi from the uterine muscle (figure 3 A&B). Placental sections of group P (figure 3 C&D) showed chorionic villi lie on fibrin layer separating it from uterine muscle without intervening decidua.

Simple Linear Regression analysis was carried out to predict the level of placental expression of VCAM-1 based upon the circulating VCAM-1 level and it showed a significant regression equation (F= (1,60) = 149.016, P <0.000) with an R² of 0.713. Placental expression of VCAM-1 increased by 0.389 ng/mg for each 0.032 ng/ml increase of serum VCAM-1 level.

DISCUSSION

Placenta accreta (PA) is abnormal adherence of the placenta to the myometrium and is associated with life-threatening blood loss. Enhanced angiogenesis and massive trophoblastic invasion are the underlying pathological mechanisms for PA. Our study hypothesized that serum VCAM-1 may act as a predictor for the occurrence of PA and may be involved in the pathogenesis of PA through increasing trophoblastic invasion and angiogenesis. Group P exhibited substantially higher serum and placental VCAM-1 levels than group N. our result concoid with the results of Korkmazer et al⁵ who showed that the placental expression of VCAM-1 was significantly high in case of PA compared to normal pregnancy⁵.

Pregnancy-associated expression of circulating VCAM-1 is attributed to direct production from placental trophoblastic cells¹¹ and endothelial production under the influence of the increased pro-inflammatory cytokines such as Tumor necrosis factor-α (TNF-α) and Interleukin-1β (IL-1β)¹²,¹³. The rise of VCAM-1 in the PA group could be clarified by the amplified inflammatory condition associated with PA, in the form of increased activation of macrophages that in turn increase the production of both local and circulating VCAM-1. In pregnancy, VCAM-1 plays a vital role in maternal immune tolerance that hinders fetal immunological rejection¹⁵. Moreover, VCAM-1 plays a crucial role in placentation through the promotion of trophoblastic invasion by its pro-angiogenic and cellular adhesion effects. Furthermore, VCAM-1/α4 integrin pathway plays an important role in inflammatory stimuli-induced angiogenesis, which is responsible for placental blood flow during implantation¹⁶.

Distinctly, serum VCAM-1 level during the 2nd trimester had significant higher levels than those of the 3rd trimester. Our results are supported by the results of Raynor and Parthasarathy¹¹ and Daniel et al¹⁷ who showed that serum levels of VCAM-1 were inversely proportional to gestational age¹¹,¹⁷. Although, Austgulen et al¹⁸ suggested that serum VCAM-1 increases with gestational age in preeclamptic patients, due to the associated vascular endothelium dysfunction¹⁸. Our results of decreasing serum VCAM-1 level along the progress of pregnancy is explained by down-regulation of its production from placental trophoblast at term. This decrement of VCAM-1 production helps trophoblastic separation to achieve delivery¹⁹,²⁰.

Remarkably, this study investigated the predictive value of 2nd trimester serum VCAM-1 levels, and the results showed that a high VCAM-1 level ≥ 79.89 ng/ml can predict the occurrence of PA with a sensitivity of 93.5% and a specificity of 96.8%.
CONCLUSION

Conclusively, the results of VCAM-1 analysis suggested that serum VCAM-1 levels were higher in case of PA than those of normal pregnancy and it had a significant predictive value for PA with markedly high sensitivity and specificity. Therefore, we suggest that detection of its high level in the 2nd trimester can predict the occurrence of PA in healthy women. Moreover, placental VCAM-1 may be implicated in the pathogenesis of PA by enhancing trophoblastic invasion through the promotion of angiogenesis.

REFERENCE


Table (1): Mean values of serum levels of VCAM-1 of all study groups (n = 31):

Data were expressed as means ± standard error. N\textsubscript{T2}: Pregnant women with normal placenta in 2\textsuperscript{nd} trimester, N\textsubscript{T3}:

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Group N</th>
<th>Group P</th>
<th>Inter-groups comparison P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2\textsuperscript{nd} trimester</td>
<td>3\textsuperscript{rd} trimester</td>
<td>P-Value</td>
</tr>
<tr>
<td>VCAM-1</td>
<td>31.211 ± 3.814 ng/ml</td>
<td>10.983 ± 0.147 ng/ml</td>
<td>0.000*</td>
</tr>
</tbody>
</table>

pregnant women with normal placenta in 3\textsuperscript{rd} trimester, P\textsubscript{T2} pregnant women with PA in 2\textsuperscript{nd} trimester, P\textsubscript{T3} pregnant women with PA in 3\textsuperscript{rd} trimester.

*: statistically significant difference (P-value ≤ 0.05).

Table (2): Mean values of placental tissue VCAM-1 levels of both normal pregnancy group and placenta accreta (PA) group (n = 31):

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Group N</th>
<th>Group P</th>
<th>P- value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VCAM-1</td>
<td>2.901 ± 0.096 ng/mg protein</td>
<td>41.911 ± 1.885 ng/mg protein</td>
<td>0.000*</td>
</tr>
</tbody>
</table>

Data were expressed as means ± standard error.

*: statistically significant difference (P-value ≤ 0.05).

Table (3): Receiver operator characteristic (ROC) curve showed the area under the curve (AUC)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>AUC, 95%CI</th>
<th>P-value</th>
<th>+PV</th>
<th>-PV</th>
<th>Cutoff point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal placenta versus placenta accreta</td>
<td>93.5%</td>
<td>96.8%</td>
<td>0.925</td>
<td>&lt; 0.001</td>
<td>96.7</td>
<td>93.7</td>
<td>79.89 ng/ml</td>
</tr>
</tbody>
</table>

and the predictive value of 2\textsuperscript{nd} trimester serum VCAM-1 levels:

AUC: area under the curve, CI: confidence interval, +PV: positive predictive value, -PV: negative predictive value.

P-value ≤ 0.05 is considered statistically significant.
Figure (1): Serum levels of VCAM-1 of both normal pregnancy groups (2\textsuperscript{nd} trimester and 3\textsuperscript{rd} trimester) and PA groups (2\textsuperscript{nd} trimester and 3\textsuperscript{rd} trimester).

P-value < 0.05 is considered statistically significant.

*: statistically significant difference compared to normal 2\textsuperscript{nd} trimester group.

#: statistically significant difference compared to normal 3\textsuperscript{rd} trimester group.

+: statistically significant difference compared to PA 2\textsuperscript{nd} trimester group.

Figure (2): A receiver operator characteristic (ROC) curve for 2\textsuperscript{nd} trimester serum VCAM-1 levels.
Figure (3): (A&B): Normal placenta: Hematoxylin and eosin-stained sections showing the decidua (brown asterisk) is attached to the basal plate of chorionic villi (black arrows) (40x, 100x respectively). (C&D): Placenta accreta: Hematoxylin and eosin-stained sections showing chorionic villi (black arrow) lie on the fibrin layer, that separates it from the muscle layer (blue arrowhead) without intervening decidua (40x, 100x respectively).