Relation of inflammatory markers with both presence and severity of hyperemesis gravidarum

Związek pomiędzy markerami stanu zapalnego a obecnością i nasileniem wymiotów ciężarnych

Raziye Keskin Kurt, Ayşe Güler, Dilek Benk Silfeler, Mustafa Doğan Özçil, Atilla Karateke, Ali Ulvi Hakverdi,

Abstract

Objectives: The aim of our study is to determine the newly introduced systemic inflammation marker, neutrophil lymphocyte ratio (NLR) in hyperemesis gravidarum (HG) patients and to investigate the association between severity of the disease and NLR.

Method: The study population consisted of 55 pregnant patients with HG and 50 pregnant women without complaints matched for gestational age as a control group. The HG patients were grouped as mild (n=16), moderate (n=19) and severe (n=20) according to Modified Pregnancy- Unique Quantification of Emesis and Nausea Scoring Index Questionnaire. Furthermore, hsCRP, neutrophils, lymphocytes, and NLR were evaluated with complete blood count.

Results: The HG group had significantly higher NLR values compared to the control group (2.69±1.81 vs 1.97±1.34, p=0.004). HsCRP levels were significantly higher among HG patients compared to the control group (1.95±2.2 vs 0.56±0.30, p<0.001). The subgroup analysis revealed statistically significant increases in NLR and hsCRP values with increased HG severity (p<0.001, p=0.002). The correlation analysis demonstrated a strong correlation between NLR and hsCRP levels (r: 0.703, p<0.001).

Conclusion: Our study results showed that NLR and hsCRP levels are increased in HG disease compared to gestational age matched control group subjects. Furthermore, NLR and hsCRP values are correlated with severity of disease. NLR could be used as a marker for both presence and severity of hyperemesis gravidarum.

Key words: hyperemesis gravidarum / inflammation / neutrophil to lymphocyte ratio / hsCRP /

Streszczenie

Cel pracy: Celem pracy była ocena nowo wprowadzonych markerów stanu zapalnego, wskaźnika neutrofili do limfocytów (NLR) u ciężarnych z wymiotami (HG) oraz zbadanie powiązań między ciężkością choroby a NLR.

Key words: hiperemoesis gravidarum / zapalenie / neutrofili do limfocytów / hsCRP /
Wnioski: nasze badanie pokazuje, że poziom NLR i hsCRP jest zwiększony u pacjentek z wymiotami ciążowymi w porównaniu do zdrowych ciężarnych w tych samych tygodniach ciąży. Co więcej, NLR i hsCRP korelują z nasileniem choroby. NLR może być markerem obecności i ciężkości wymiotów ciążarniących.

Słowa kluczowe: wymiery ciążarniany / zapalenie / wskaźnik neutrofile / limfocyty / hsCRP /
Table 1. Modified Pregnancy- Unique Quantification of Emesis and Nausea Scoring Index Questionnaire.

<table>
<thead>
<tr>
<th>Question</th>
<th>Score 1</th>
<th>Score 2</th>
<th>Score 3</th>
<th>Score 4</th>
<th>Score 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. On average in a day, for how long do you feel nauseated or sick to your stomach?</td>
<td>Not at all</td>
<td>1 hr</td>
<td>2-3 hr</td>
<td>4-6 hr</td>
<td>6 hr</td>
</tr>
<tr>
<td>(1)</td>
<td>(2)</td>
<td>(3)</td>
<td>(4)</td>
<td>(5)</td>
<td></td>
</tr>
<tr>
<td>2. On average in a day, how many times do you vomit or thrown up?</td>
<td>7 times</td>
<td>5-6 times</td>
<td>3-4 times</td>
<td>1-2 times</td>
<td>I did not throw up</td>
</tr>
<tr>
<td>(5)</td>
<td>(4)</td>
<td>(3)</td>
<td>(2)</td>
<td>(1)</td>
<td></td>
</tr>
<tr>
<td>3. On average in a day, how many times do you have retching or dry heaves without bringing anything up?</td>
<td>None</td>
<td>1-2 times</td>
<td>3-4 times</td>
<td>5-6 times</td>
<td>7 times</td>
</tr>
<tr>
<td>(1)</td>
<td>(2)</td>
<td>(3)</td>
<td>(4)</td>
<td>(5)</td>
<td></td>
</tr>
</tbody>
</table>

Total score (sum of replies to 1, 2, and 3): mild NVP, 6; moderate NVP, 7-12; severe NVP, >13.
NVP: nausea and vomiting of pregnancy.

Figure 1. Comparison of NLR levels in the control and HG subgroups.

Figure 2. The correlation of NLR and hs-CRP in the population.

Statistics
Numerical variables were expressed as mean ± standard deviation, and categorical variables as percentage. Numerical variables with normal distribution were compared using student's t-test for the paired groups and one-way ANOVA (analysis of variance) for triplet groups while numerical variables with abnormal distribution were compared using Mann Whitney-U test for the paired groups and Kruskal-Wallis test for triplet groups. Tukey's test was chosen as the post-hoc test for ANOVA. Categorical variables were evaluated using chi-square test. Normality of distribution was assessed with Kolmogorov Smirnov test for numerical variables. The correlation between variables was evaluated using Pearson's correlation test. SPSS 20.0 package software (SPSS inch, Chicago, Illinois, USA) was used for the statistical analysis.

Results
Mean age was 29±2.8 years among the patients with HG included in the study whereas it was 30±3.1 years for the control group. BMI was 23.5±3.1 in the HG group and 24.3±3.3 in the control group. No statistically significant difference was found between the patients and the control group regarding age, parity, gestational age and BMI. Baseline characteristics and biochemical values are summarized in Table II.

HsCRP levels were significantly higher among HG patients compared to the control group (1.95±2.2 vs 0.56±0.30, p<0.001).

The HG group had significantly higher NLR values compared to the control group (2.69±1.81 vs 1.97±1.34, p=0.004) (Figure 1). The subgroup analysis revealed statistically significant increases in NLR and hs-CRP values with increased HG severity (p<0.001, p=0.002, respectively) (Table III). The correlation analysis demonstrated a strong correlation between NLR and hsCRP levels (r: 0.703, p<0.001) (Figure 2).
Table II. Baseline clinical and laboratory characteristics of patient and control groups.

<table>
<thead>
<tr>
<th></th>
<th>HG patients (n:55)</th>
<th>Control (n:50)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>29±2.8</td>
<td>30±3.1</td>
<td>0.092</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.5±3.1</td>
<td>24.3±3.3</td>
<td>0.194</td>
</tr>
<tr>
<td>Gestational Age (weeks)</td>
<td>9.4±3</td>
<td>8.8±2.5</td>
<td>0.413</td>
</tr>
<tr>
<td>Parity</td>
<td>2.1±0.5</td>
<td>2.4±0.6</td>
<td>0.441</td>
</tr>
<tr>
<td>Hscrp (mg/l)</td>
<td>1.95±2.2</td>
<td>0.56±0.30</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Leukocyte (x1000/ mm³)</td>
<td>7.58±1.95</td>
<td>6.32±1.33</td>
<td>0.001</td>
</tr>
<tr>
<td>Neutrophil (x1000/ mm³)</td>
<td>4.78±1.45</td>
<td>3.68±1.30</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lymphocyte (x1000/ mm³)</td>
<td>2.12±0.66</td>
<td>2.3±0.81</td>
<td>0.213</td>
</tr>
<tr>
<td>NLR</td>
<td>2.69±1.81</td>
<td>1.97±1.34</td>
<td>0.004</td>
</tr>
</tbody>
</table>

BMI: body mass index, NLR: neutrophil to lymphocyte ratio, HG: hyperemesis gravidarum

Table III. Clinic and laboratory findings according to the of patient subgroups.

<table>
<thead>
<tr>
<th></th>
<th>Mild (n:16)</th>
<th>Moderate (n:19)</th>
<th>Severe (n:20)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>29.8±3.4</td>
<td>28.7±2.9</td>
<td>28.8±2.2</td>
<td>0.472</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.4±2.4</td>
<td>23.8±3.2</td>
<td>24.1±3.1</td>
<td>0.254</td>
</tr>
<tr>
<td>Gestational Age (weeks)</td>
<td>9.0±0.5</td>
<td>9.8±3.3</td>
<td>9.3±2.2</td>
<td>0.710</td>
</tr>
<tr>
<td>Hscrp (mg/l)</td>
<td>0.96±0.44</td>
<td>1.52±0.82</td>
<td>3.15±3.24</td>
<td>0.005</td>
</tr>
<tr>
<td>Leukocyte (x1000/ mm³)</td>
<td>7.0±2.1</td>
<td>7.8±1.76</td>
<td>7.9±1.9</td>
<td>0.355</td>
</tr>
<tr>
<td>Neutrophil (x1000/ mm³)</td>
<td>3.45±0.63</td>
<td>4.72±0.99</td>
<td>5.89±1.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lymphocyte (x1000/ mm³)</td>
<td>2.26±0.52</td>
<td>2.29±0.66</td>
<td>1.85±0.71</td>
<td>0.076</td>
</tr>
<tr>
<td>NLR</td>
<td>1.62±0.58</td>
<td>2.34±1.23</td>
<td>3.87±2.26</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

BMI: body mass index, NLR: neutrophil to lymphocyte ratio

Discussion

Our study results showed for the first time in the literature that NLR and hsCRP levels are increased in patients with HG compared to control subjects matched for gestational age. Furthermore, NLR and hsCRP values are correlated with severity of the disease.

HG is a condition that adversely affects quality of life in pregnant women [20]. Severe nausea and vomiting is the 3rd most common cause of hospitalization during pregnancy [21]. Nausea and vomiting seen during the first trimester causes serious workforce loss among women [22]. In addition to the morbidity, HG may rarely lead to conditions with high mortality risk such as Wernicke's encephalopathy and central pontine myelinolysis [23]. It is therefore important to provide appropriate treatment; however, the current treatment of HG is empirical and suboptimal as the exact etiology remains unknown. Several mechanisms have been suggested to be involved in the etiopathogenesis of HG; however, none of them alone has provided a full explanation and the etiology therefore appears to be multifactorial [24].

Inflammation is thought to be playing an important role in the pathophysiological mechanism of HG [11, 12]. Yoneyama et al. demonstrated increased TNF-α levels in HG [25]. Besides Kaplan et al. revealed that TNF-α, a biologically active cytokine involved in immune disorders, may be associated with the pathogenesis and progression of hyperemesis gravidarum [13]. In addition, Kuscu et al. have shown increased levels of the inflammation marker, IL-6 in hyperemesis. They proposed that immunological activity seen in patients with HG and the dramatic response to short-term treatment with anti-inflammatory drugs (steroid therapy) may be the clues to consider HG as an inflammatory response during pregnancy [9]. Verit et al. found decreased levels of paraoxonase-1 in patients with HG and correlated this finding to increased oxidative stress and inflammation in HG, and they also demonstrated increased levels of the inflammatory marker, hsCRP in patients with HG [12]. Engin-ustun et al. showed increased CRP and vaspin levels in patients with HG and associated this finding with inflammation [11]. In the present study, the inflammation markers, hsCRP and NLR were found to be increased, supporting the role of inflammation in HG etiology. Furthermore, we for the first time in literature showed that hsCRP and NLR levels increase proportionally with the severity of HG.

NLR is a marker that has been recently shown to be associated with inflammation in a number of diseases [26]. Neutrophilia and lymphocytopenia are physiological responses of the immune system to various conditions including systemic inflammation and malignancy. Cho S et al. found increased NLR levels in endometriosis which is a chronic condition associated with inflammation, and highlighted that NLR may be a simple and readily available marker for the diagnosis of endometriosis [27]. Cho et al. showed increased NLR levels in epithelial ovarian cancer as a measure of the systemic inflammatory response, and demonstrated further increases in NLR with increasing stages of the disease [28]. Kim et al. showed superiority of NLR plus cervix length combination to cervix length alone in
predicting pre-term pregnancy, which is an obstetric condition associated with inflammation [29]. Granulocyte levels increase while lymphocyte levels decrease in later stages of pregnancy. Minagawa et al. found significantly increased granulocyte levels in HG, and showed that lymphocyte levels were decreased compared to normal pregnancy although the difference was not statistically significant [10]. Similar to the findings of Minagawa et al., we found increased neutrophil levels in the present study, and we for the first time showed that the inflammation marker, NLR also increases in HG.

Conclusion

In conclusion, NLR could be used as a marker for both presence and severity of hyperemesis gravidarum. HG patients have increased levels of hsCRP and NLR, indicating that inflammation may play an important role in the pathogenesis of the disease. Furthermore, NLR and CRP levels increase even further with the increasing severity of the disease. Although the association between HG and NLR remains unclear, we believe that the activation of inflammation associated with HG lead to increased NLR values. Nevertheless, further studies are required in order to fully understand the exact pathogenesis of HG.

NLR could be a marker in hyperemesis gravidarum.

Limitations

One of the major limitations of the present study is the relatively low number of patients. Additionally, hsCRP and NLR have been assessed as inflammatory markers whereas TNF-alpha and interleukin levels were not determined in the present study. Furthermore, it remains unclear whether the increase in inflammatory marker levels observed in HG is the underlying cause of the condition, or a result of the compensatory mechanism in response to HG [13]. The possibility that it may be a mere effect of disturbances connected with emesis and not its cause, needs to be taken into consideration as well.

Authors’ Contribution

1. Razye Keskin Kurt – concept, analysis and interpretation of data, article draft, corresponding author.
3. Dilok Benik Sifteker – study design, acquisition of data, article draft, analysis and interpretation of data.
4. Mustafa Doğan Özöl – concept, analysis and interpretation of data, acquisition of data.
5. Atilla Karateke – revised article critically, acquisition of data, study design, article draft.
6. Ali Ulvi Halverdi – revised article critically, analysis and interpretation of data, article draft.

Authors’ statement

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References