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# Relationship between changes in hemoglobin level in cesarean section and delta neutrophil index

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## ABSTRACT

**Aims:** Accurate prediction of changes in hemoglobin (Hb) levels, an indicator of blood loss, in cesarean deliveries is critical for reducing maternal morbidity and mortality. This study evaluated the potential relationship between the preoperative delta neutrophil index (DNI), an inflammatory marker, and changes in Hb levels after cesarean section.

**Methods:** Women with a history of a single cesarean section and who underwent a second cesarean section for delivery between 2018 and 2020 were retrospectively analyzed. The difference between the preoperative and postoperative 6$^{th}$-hour and 24$^{th}$-hour Hb levels was defined as the delta Hb 1 (ΔHb1) level and delta Hb 2 (ΔHb2) level, respectively. The primary outcome was the relationship between preoperative DNI with ΔHb1 level and ΔHb2 level. We also investigated the relationships of the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) with DNI and changes in Hb levels.

**Results:** The study included 368 women with a mean age of 28 (19 to 45) years. The mean DNI was -0.82±5.62, NLR was 4.31±2.16, and PLR was 141.89±55.22. A positive correlation was found between DNI and ΔHb1 level ($r=0.624$, $p<0.05$) and ΔHb2 level ($r=0.372$, $p=0.05$). No significant correlation was found between PLR and NLR.

**Conclusions:** Among women who underwent cesarean section, preoperative DNI showed a positive relationship with changes in postoperative Hb levels. The significance of DNI in predicting changes in Hb levels after cesarean section needs to be explored.

## Introduction

Early diagnosis of pregnancies at high risk for postpartum hemorrhage, timely interventions to prevent intrapartum hemorrhage and appropriate treatment are key in reducing maternal morbidity and mortality (1). Yefet et al. (2) showed that a decrease in hemoglobin (Hb) of ≥2 g/dL was compatible with the diagnosis of postpartum hemorrhage, and the maximum rate of decrease in Hb exchange as a laboratory indicator of blood loss is in the first 6-12 hours after birth, reaching a plateau in 24-48 hours. Therefore, it is important for clinicians not to miss the possible intrapartum and postpartum blood losses, as well as the follow-up of postpartum changes in Hb level and the prediction of possible over-falls.

Inflammation and inflammatory conditions are common in gynecology and obstetrics. Chorioamnionitis, inflammation of the umbilical vessels (umbilical vasculitis), and funisitis are

common in patients undergoing postpartum hysterectomy due to postpartum hemorrhage (3). To this end, numerous inflammatory markers have been studied in gynecology and obstetrics, and studies focusing on cost-effective markers have increased. Recently, the focus has shifted to the delta neutrophil index (DNI), which indicates the number of immature granulocytes in complete blood count (CBC) from peripheral venous blood (4). DNI reflects the ratio of immature granulocytes to the total neutrophil count and is known to be associated with infection and inflammation (5) and may be predictive in various infectious diseases such as peritonitis, bacterial infections, and sepsis (6-8). Previously, DNI was associated with preeclampsia and eclampsia in obstetrics (9,10) and was considered a histopathological marker for chorioamnionitis in pregnant women with a rupture of membranes (10).

CBC shows systemic inflammation and hemostasis (11). CBC parameters like neutrophil-to-lymphocyte ratio (NLR) (12) and platelet-to-lymphocyte ratio (PLR) (13) are easily assessable markers that can be associated with prognosis in various diseases.

Recently, postpartum hemorrhage has been redefined as a cumulative blood loss of 1,000 mL or more or any blood loss associated with the signs and symptoms of hypovolemia, regardless of the delivery route (14). It is clinically advantageous to predict changes in Hb levels as an indicator of blood loss (2,11). Consequently, we examined the relationship between preoperative DNI and postoperative changes in Hb levels in pregnant women undergoing cesarean section.

## Methods

### Study population

This retrospective study was conducted at the Etlik Zübeyde Hanım Maternity and Women's Health Training and Research Hospital. Women with a previous history of one cesarean section and who underwent a second cesarean section between January 2018 and January 2020 were identified from the hospital's registration system and those who underwent a second cesarean delivery at 37-42 weeks of gestation were included. To obtain a more homogeneous cohort, we included only cesarean deliveries performed with a lower segment transverse incision in the abdomen with a Pfannenstiel incision as a standard procedure. Patients with a history of multiple (>1) cesarean section, multiple pregnancies, fetal anomalies, pregnancies followed in the perinatology department, maternal comorbidity, preterm and post-term pregnancies, and placental invasion anomalies were excluded. Additionally, to exclude potential confounding factors with DNI, women with signs of systemic infection during hospitalization (e.g., cystitis, tonsillitis, influenza, prolonged rupture of membranes), preoperative infection using anticoagulants and antiaggregators, who developed drug-dependent hemolysis, or with hematological diseases were excluded. Ethical approval was obtained from the Etlik Zübeyde Hanım Maternity and Women's Health Training and Research Hospital Local Ethics Committee (06.08.2020-12).

### Laboratory and instrumental investigations

An initial hemogram test is routine in all hospitalized patients at our center. Hemograms are also routine at the 6$^{th}$ and 24$^{th}$ hour postoperatively in patients undergoing cesarean section. DNI was obtained using an automated cell analyzer (ADVIA 2120 Hematology System, Siemens, Healthcare Diagnostics, Forchheim, Germany). This flow cytometer-sensitive hematological analyzer uses two independent methods to count leukocytes: myeloperoxidase and the lobule/nuclear density channel. The DNI is calculated using the following formula: (leukocyte subfraction measured by the cytochemical reaction in the myeloperoxidase channel) – (leukocyte subfraction measured by the weak radiation reflectance in the nuclear lobular channel) (10,15). Hemograms were analyzed using a MINDRAY BC-6000 (Mindray, China). NLR was calculated by dividing the neutrophil count by the lymphocyte count, and PLR was calculated by dividing the platelet count by the lymphocyte count. DNI, PLR, and NLR were obtained from the initial CBC test during hospitalization.

The delta Hb 1 (ΔHb1) level was calculated by subtracting the Hb levels at the postoperative 6$^{th}$ hour from the initial Hb values on admission. The delta Hb 2 (ΔHb2) level was calculated by subtracting the Hb levels at the postpartum 24$^{th}$ hour from the initial Hb values on admission. Demographics, age, obstetric history, body mass index (BMI) (kg/m$^2$), and neonatal data (birth weight, sex) were recorded. The primary outcome was the relationship of DNI with ΔHb1 level and ΔHb2 level, corresponding to the amount of blood loss during cesarean section. As secondary outcomes, NLR and PLR were also investigated for their relationship with ΔHb1 level and ΔHb2 level.

### Statistical Analysis

All analyses were performed using Statistical Package for Social Sciences (SPSS) (version 20; IBM Corp., Armonk, NY, USA). After testing the normality assumptions, the variables were expressed as median and minimum-maximum (min-max), mean±standard deviation, or frequency (%). The t-test or Mann-Whitney test was used to compare numerical data based on the normality analyses. The relationships between continuous variables were analyzed using Pearson correlation analysis. $P<0.05$ was considered statistically significant.

## Results

The study included 368 women [mean age: 28 (19 to 45)] years. The mean birth weight was 3380 (2450 to 4900) g, and

the mean birth week was 39 (37 to 40). The mean BMI was 30 (22 to 39) kg/m$^2$. The male-to-female ratio of the fetuses was 51.1/48.9% (Table 1).

The mean DNI in the preoperative period was -0.82±5.62. The mean Hb value in the preoperative blood counts was 11.69±1.40 g/dL. The mean Hb value at the 6$^{th}$ hour after the cesarean section was 10.32±1.33 g/dL and 10.09±1.29 g/dL at the 24$^{th}$ hour. The mean ΔHb1 level was 1.37 and the mean ΔHb2 level was 1.6. The mean PLR was 141.89±55.22, and the mean NLR was 4.31±2.16 (Table 2).

A positive correlation was observed between DNI and ΔHb1 level (r=0.624, p<0.001) and ΔHb2 level (r=0.372, p<0.001) (Table 3). No correlation of PLR or NLR with ΔHb1 level and ΔHb2 level was noted.

**Table 1. Demographic and obstetrics data of the cases in the study (n=368)**

| | |
|---|---|
| Age, median (min-max) | 28 (19-45) |
| Body mass index (kg/m²), median (min-max) | 30 (22-39) |
| Gravida, median (min-max) | 2 (2-9) |
| Parity, median (min-max) | 1 (1-5) |
| Placental localization, n (%) | |
| Anterior | 242 (65.8) |
| Posterior | 109 (29.6) |
| Fundal | 17 (4.6) |
| Birth week, median (min-max) | 39 (37-40) |
| Birth weight (g), median (min-max) | 3380 (2450-4900) |
| Sex of the newborn, n (%) | |
| Female | 180 (48.9) |
| Male | 188 (51.1) |

min-max: Minimum-maximum

**Table 2. Hemogram test results of the cases in the study (n=368)**

| | |
|---|---|
| Hemoglobin initial value (g/dL), mean±SD | 11.69±1.40 |
| Hemoglobin 6$^{th}$ hour (g/dL), mean±SD | 10.32±1.33 |
| Hemoglobin 24$^{th}$ hour (g/dL), mean±SD | 10.09±1.29 |
| Delta hemoglobin 1 (g/dL), mean±SD | 1.37±0.83 |
| Delta hemoglobin 2 (g/dL), mean±SD | 1.60±0.93 |
| Platelet lymphocyte ratio (%), mean±SD | 141.89±55.22 |
| Neutrophil lymphocyte ratio (%), mean±SD | 4.31±2.16 |
| Delta neutrophil index, mean±SD | -0.82±5.62 |

SD: Standard deviation

## Discussion

Accurate prediction and early diagnosis of blood loss in cesarean deliveries can help clinicians arrange timely interventions and appropriate management to prevent morbidity and mortality (1). We examined the relationship between preoperative DIN and changes in Hb levels before and after cesarean section. We observed that DNI increased significantly in patients with larger differences in pre-and postoperative Hb levels. There was no correlation between ΔHb1 level, ΔHb2 level, and PLR or NLR. However, a positive correlation was found between DNI and ΔHb1 level or ΔHb2 level. To the best of our knowledge, this is the first study to use DNI to assess changes in Hb associated with the amount of blood loss.

Postpartum hemorrhage occupies an important place in obstetric practice as it is a frequent cause of maternal mortality in developing countries (16,17). To reduce maternal mortality, prenatal education and the availability of an experienced team with a multidisciplinary approach are crucial for pregnancies with risk factors for obstetric hemorrhage. A European-based study found that the risk of hysterectomy after cesarean section was nine-fold higher (18). Therefore, clinicians need to predict the risk of bleeding after cesarean section, and it is essential to take the necessary precautions for such an event. Unfortunately, there are no known risk factors for blood loss due to postpartum and intrapartum hemorrhage, especially for most cases of uterine atony; therefore, a substantial proportion of hemorrhages occurs in the absence of recognized risk factors (19). Although inflammation in the uterus and placenta appears to be associated with postpartum hemorrhage due to inadequate contractility of the myometrium, the exact mechanism is not clear (20). Inflammation also supports the formation of residual placenta and placental invasion abnormalities, which pose a significant risk for uterine atony (21). Inflammation, endothelial damage, infarcts, fibrotic villi, and placental septal cysts dramatically increase in the residual placenta. In addition, placental inflammation and decidual defects between uterine smooth muscle fibers are present in placental invasion abnormalities, which carry a very high risk of postpartum hemorrhage (22).

An increase in the immature/total granulocyte ratio resulting from incomplete maturity of circulating neutrophils during inflammation and an increase in neutrophil banding is named left shift and, is used to demonstrate systemic inflammatory responses (23). DNI, which indicates the percentage of immature granulocytes in the cardiovascular system by a dissimilar method, is considered an indicator of inflammation.

**Table 3. Investigation of the relationship between hemogram values and delta neutrophil index in pregnant women**

| | Platelet-lymphocyte ratio | Neutrophil-lymphocyte ratio | Delta neutrophil index |
|---|---|---|---|
| Delta hemoglobin 1 | 0.28*/-0.056** | 0.31*/0.052** | **<0.001*/0.624**** |
| Delta hemoglobin 2 | 0.67*/-0.022** | 0.38*/0.046** | **<0.001*/0.372**** |

*p value; **r value; Pearson correlation test, bold is statistically significant

It has been shown to predict pneumonia and acute appendicitis as well as sepsis in adult and pediatric populations (3,7). It was reported to predict chorioamnionitis with a sensitivity and specificity of 93% at a cut-off of 1, making DNI a more potent parameter than other commonly used maternal serum markers in predicting chorioamnionitis (24). Cho et al. (9) showed that DNI could be used as a serum marker to predict chorioamnionitis in patients with preterm premature rupture of membranes, and lymphocyte count, C-reactive protein, and DNI could be used to predict inflammatory responses in the placenta. A meta-analysis reported the high diagnostic accuracy of DNI as a predictive and prognostic factor in infected patients (7). Additionally, DNI was shown to be an effective parameter in estimating the mortality of these patients and suggested to be useful in clinical practice (25).

In a study with 278 patients that defined massive transfusion as a transfusion of ≥10 units of red blood cells within 24 hours after postpartum hemorrhage, massive transfusion was detected in 60 participants (26). In the current study, an optimal cut-off value of 3.3 for DNI was found to be significantly associated with an increased risk of massive transfusion (with an AUC of 0.74), as well as a cut-off value of 3.54 for PLR and 0.48 for NLR (26). In addition, Kong et al. (27) demonstrated that the optimal cut-off value of DNI was 1 at admission and 2.6 on day 1 to predict 30-day mortality in patients with upper gastrointestinal bleeding. Considering the results of these studies (26,27), DNI is seen as a parameter related to the amount of blood loss, the need for transfusion, and mortality due to blood loss. We found a positive correlation between preoperative DNI and ΔHb1 level and ΔHb2 level.

The strength of the current study is the investigation of the relationship between changes in postpartum Hb levels and widely recognized markers DNI, PLR, and NLR in a homogeneous group of patients undergoing cesarean section. In addition, most potential causes that may affect these markers were excluded. The large sample size reflected its high statistical power. A limitation of the study is that DNI is a hematological marker that may not be useful in each patient. Because postpartum hemorrhage can be associated with various factors, DNI may be misleading in comorbid conditions. The most important factor in preventing postpartum hemorrhage is to be cautious of the risk and to take the necessary measures early (1,13,14). However, predicting the risk of blood loss in the preoperative period is not easy. Based on the data obtained in our study, DNI may help predict the extent of blood loss during cesarean section and thus can assist the physician in taking the necessary precautions.

## Conclusion

This study found a positive correlation between DNI and changes in Hb levels at the 6$^{th}$ and 12$^{th}$ h in the post-cesarean period.

### Ethics

**Ethics Committee Approval:** The study was approved by Etlik Zübeyde Hanım Maternity and Women's Health Training and Research Hospital Local Ethics Committee (decision no: 12, date: 06.05.2020). The study protocol was in accordance with the Declaration of Helsinki on the ethical conduct of studies involving human subjects.

**Informed Consent:** All study participants provided written informed consent.

### Authorship Contributions

Surgical and Medical Practices: Y.A.R., E.N.V., F.B.F., R.S.K. Concept: Y.A.R., A.A., Design: Y.A.R., A.A., E.N.V., Data Collection or Processing: E.N.V., H.E.T., Analysis or Interpretation: Y.A.R., E.N.V., R.E.P. Literature Search: Y.A.R., A.A., E.N.V. Writing: Y.A.R., A.A., E.N.V., F.B.F., H.E.T., S.Y.E., R.E.P., R.S.K.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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