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Novel marker to predict rupture risk in tubal ectopic pregnancies: the systemic immune-inflammation index

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ABSTRACT

Objectives: Ectopic pregnancy is a life-threatening condition; delaying treatment can result in mortality or serious complications. Identification of a biomarker that can predict tubal rupture may be helpful for guiding treatment. In this study, we evaluated the association between serum β-hCG, biochemical markers, Systemic Immunity-inflammation Index (SII) score, and the trophoblastic invasion stage.

Material and methods: Tubal pregnancy was classified into three groups based on the depth of trophoblastic infiltration: stage I — limited to the mucosa; stage II — invaded the muscular layer, and stage III — invaded the serosa/subserosa of the tuba uterine. The association between groups, serum β-hCG, biochemical markers, and the SII score were assessed.

Results: There was no significant difference between the groups, hemoglobin, platelet count, MPV, RDW, NLR or PLR values ($p > 0.05$). A ROC analysis was performed to evaluate the accuracy of serum β-hCG predictions for infiltration level. At a 95% confidence interval upper limit, cut-off value of the serum β-hCG that best predicted stage III trophoblastic infiltration, was 2799 mIU/mL, with 78.9% sensitivity, 53.8% specificity (positive predictive value was 71.4%, and a negative predictive value was 63.6%). Moreover, ROC curve analysis showed that The SII value of 792 was the best predictor of trophoblastic infiltration at stage III, with a sensitivity of 92.3% and a specificity of 63.1%.

Conclusions: A linear relationship exists between depth of trophoblastic infiltration and serum β-hCG and the SII were observed. These findings suggested that the SII score can be used for predicting tubal ectopic pregnancy rupture.

Key words: ectopic pregnancy; NLR; PLR; Systemic Immune-inflammation Index; trophoblastic invasion

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INTRODUCTION

Ectopic pregnancy (EP) is defined as the implantation of the fertilized ovum anywhere in the abdomen other than its natural location in the uterine cavity [1]. Although it is usually exhibited in a tubal location, the ovum can also be implanted in the abdomen, ovary, and cervical regions [2, 3]. Ectopic pregnancy usually causes symptoms such as abdominal pain, vaginal bleeding, and delayed menstruation [4]. Examination of the gestational sac with transvaginal ultrasonography (USG) and serum ß-hCG levels played an important role in the diagnosis.

Medical treatment is the first-line treatment for patients diagnosed in the early stages. Such medical treatment in the early stages might protect the patient from organ amputation and surgical morbidity [4, 5]. Furthermore, the success rate of medical treatment initiated in the early period is relatively high. However, in delayed cases, urgent exploration is necessary due to the increased risk of serious complications such as tuba uterine rupture and maternal death [2]. Therefore, ruptured EP is one of the most important causes of maternal mortality in the first trimester [1].

A previous study reported that levels of various inflammatory cytokines are increased in the implantation site and systemic circulation in EP patients [6, 7]. Parameters associated with angiogenesis, inflammation, and platelets and their derivatives in the immune system may represent a solution to the search for a biomarker capable of use in follow-ups of EP patients. A new index, defined as the "Systemic Immune-inflammation Index" (SII), which can be calculated using complete blood count parameters like lymphocyte, neutrophil, and platelet counts, has recently been developed. Several studies have evaluated the usefulness of this index in predicting adverse pregnancy outcomes [7, 8].

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These indices are suitable for clinical use due to their low cost and rapid results, unlike parameters such as BHCG [9], which are used to predict EP prognosis [10].

Previous studies have shown a powerful correlation between the degree of tubal wall invasion and the severity of tubal dysfunction in EP [9, 11]. However, a validated biomarker indicating the degree of trophoblastic tissue invasion into the tubal wall in patients affected by EP has not yet been identified. Determining a new, cost-effective biomarker in addition to serum ß-hCG levels and transvaginal USG in cases of EP will be useful to clinicians in terms of treatment selection and patient management.

In response to the search for biomarkers that could help predict the depth of tubal invasion, this study examined the relationship between maternal serum ß-hCG, serum biomarkers, and SII score and the depth of invasion of trophoblastic tissue into the tubal wall.

MATERIAL AND METHODS

Study design and participants

Approval for the study was granted by the Atatürk University Clinical Research Ethical Committee on 30.06.2022 (no. B.30.2. ATA.0.01.00\S44). The medical records of patients who underwent surgery with a diagnosis of ampullary tubal pregnancy at the Mengücek Gazi Training and Research Hospital, Turkey, between September 2010 and April 2022 were retrospectively examined. The study group was formed by reviewing the medical records of patients diagnosed with ampullary tubal pregnancy. The inclusion criteria were as follows: (1) ampullary pregnancy detected with surgical exploration, (2) surgical salpingectomy performed, (3) measurement of serum β-hCG prior to surgical intervention, and (4) existence of pathology reports. Exclusion criteria were as follows: (1) cases in which the entire focus of EP was not pathologically sampled, (2) cases with missing serum β-hCG and biochemical parameters data, and (3) cases with incorrect or uncertain the date the last menstrual period.

Biochemical parameters

Cases' electronic records were examined. Serum β-hCG values and transvaginal USG findings data at the time of initial presentation were collected.

Serum β-hCG were measured and transvaginal USG were applied during initial presentation of patients with clinical signs of EP. The β-hCG levels of the patients were determined with an electroluminescent immunoassay (Roche-Cobas Modular Analytics E-170; Roche Diagnostics, Germany). Blood specimens collected on admission to our clinic were placed into potassium ethylenediaminetetraacetic acid (EDTA)-containing tubes to eliminate the possibility of coagulation. All blood specimens were analyzed within 2 h using a hematology analyzer (MINDRAY BC-6800). The hematocrit (Htc), neutrophil (Neu), lymphocyte, platelet (Plt), platelet distribution width (PDW), hemoglobin (Hgb), erythrocyte distribution width (RDW), and mean platelet volume (MPV) were determined from complete blood counts. The neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) were calculated and compared between groups. SII values were calculated by SII= Plt x Neu / Lymphocyte formula [8].

Histopathological examination

All slides stained with hematoxylin and eosin (H&E) were examined by a single experienced pathologist, blinded to the patients' clinical and laboratory characteristics. Ampullary tubal pregnancy was classified based on the depth of trophoblastic infiltration [10]: Stage I — limited to the mucosa, stage II — invaded to the muscular layer, and stage III — invaded the serosa/subserosa of the tuba uterine (Fig. 1). Additional findings observed, such as bleeding, necrosis, inflammatory cell infiltration, placental villus components, decidua, and fetal elements, were also noted.

Data collection

Cases' demographic characteristics (age, parity, and risk factors for EP) were collected from medical health records.

Statistical analysis

All statistical procedures were carried out using the IBM SPSS version 25.0 software (Armonk, NY, IBM Corp, USA), with p values of 0.05 considered significant. The mean, standard deviation, and minimum-maximum values for biochemical findings were determined. The histopathological results were presented as numbers or percentages. The Shapiro-Wilk test was carried out to determine the normality of the distribution of each of the biochemical parameters. The Mann-Whitney U test was used to assess the non-normally distributed β-hCG parameter. Comparisons among invasion stages were performed using one-way ANOVA the Tukey or Games Howell tests were used as post hoc tests based on the findings of the Levene test. Receiver Operator Characteristics (ROC) curve analyses for the β-hCG and SII score among groups were performed to assess the prediction of invasion level accuracy. The following metrics were calculated: sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).

RESULTS

Thirty-three patients diagnosed with EP and followed-up at the Mengücek Gazi Training and Research Hospital between September 2010 and April 2022 were included in the study. The patients' median age was 32.9 years (range 23––40). The groups were similar in terms of gravidity and parity (Tab. 1). Histological examination revealed stage I tubal

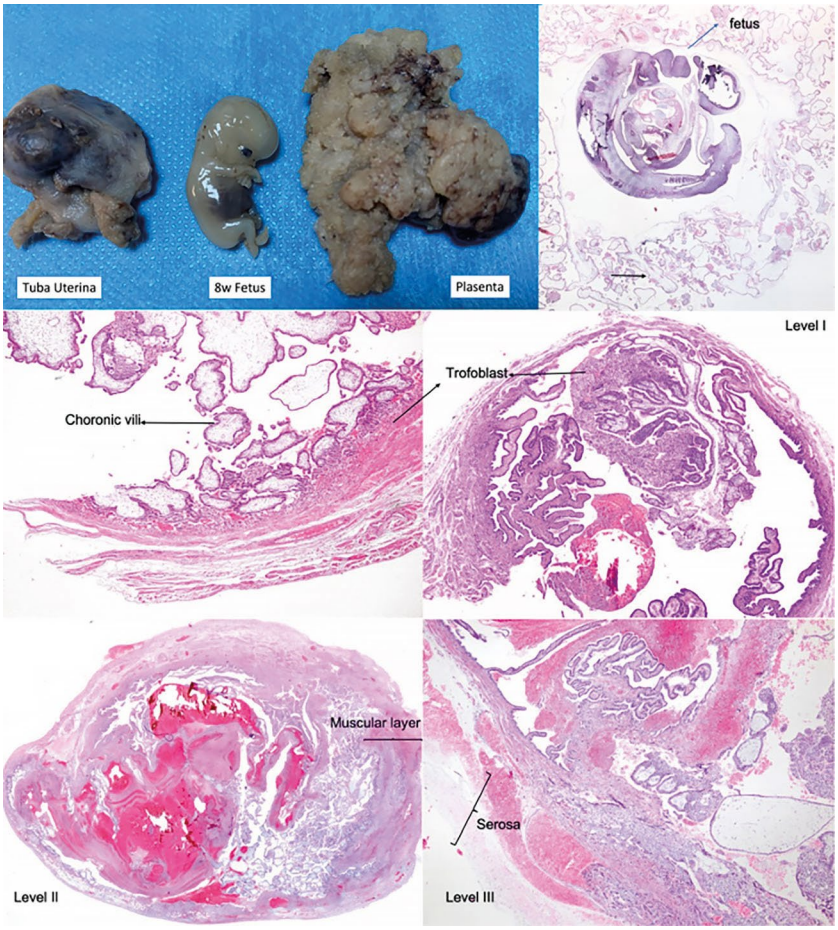

Figure 1. Macroscopic view of fetus, tuba uterine and placenta after operation of 8w ectopic pregnancy. Fetal tissue in tuba uterine. Microscopic grading of tubal invasion grading; stage I — limited to the mucosa; stage II — invaded to the muscular layer, and stage III — invaded the serosa/subserosa of the tuba uterine

Table 1. Comparison of demographic features among the groups

Baseline characteristic Mean ± SD	Stage I (n = 6)	Stage II (n = 7)	Stage III (n = 19)	Pairwise comparisons p values*	
				I–II	I–III
Age	32.6 ± 6.05	30.2 ± 6.01	33.9 ± 5.45	0.729	0.859
Gravida	3.14 ± 0.69	2.67 ± 0.82	2.84 ± 0.96	0.603	0.725
Parity	1.57 ± 1.27	1.17 ± 0.75	1.11 ± 0.74	0.688	0.462

*Indicates statistically significant difference. Statistically significant ($p < 0.05$). Analysis was done by one-way ANOVA and then Tukey or Games-Howel was used as post-hoc; SD — standard deviation; Stage I — invasion is limited to the mucosa; Stage II — invasion is limited to the muscular layer; Stage III — invasion to the subserosa or serosa; n — number of patients

infiltration in six cases (18.75%), stage II infiltration in seven (21.875%), and stage III infiltration in 19 cases (59.375%). Images of some cases that had stage I, II and III invasions are given in Figure 2.

A comparison of the groups' laboratory parameters revealed that there are no statistically significant differences between the groups' hemoglobin, platelet count, or MPV, RDW, NLR, and PLR values ($p > 0.05$). In addition, in parallel to the increase in leukocyte levels in stage III compared to stage I, the degree of trophoblastic wall invasion was also significantly higher in the stage III group than in the stage I group ($p < 0.007$) (Tab. 2). Patients with stage III infiltration had significantly higher β-hCG levels than those with stages I or II (p 0.02) (Tab. 3).

The value of β-hCG levels and the SII score as biomarkers for tubal pregnancy rupture was determined using a ROC curve analysis, and thresholds for stage III infiltration were calculated. The serum β-hCG level that best predicted stage III trophoblastic infiltration was 2799 mIU/mL, with a 95% confidence interval upper limit of 78.9% sensitivity, 53.8%

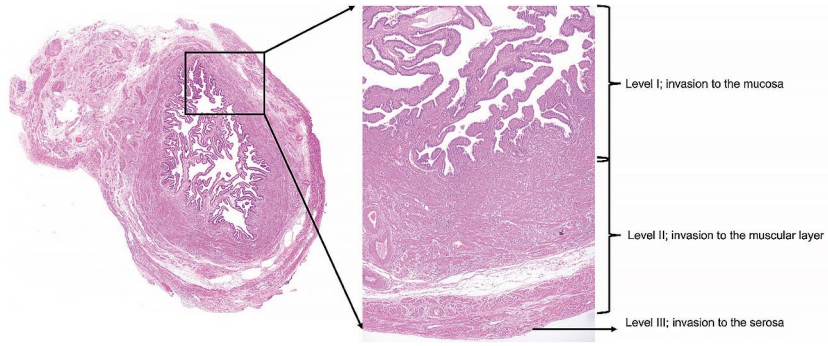

Figure 2. Classification of tubal ampullary pregnancy according to trophoblastic infiltration depth; stage I — limited to the mucosa; stage II — invaded to the muscular layer, and stage III — invaded the serosa/subserosa of the tuba uterine

Table 2. Comparison of biochemical parameters among 3 groups

Biochemical parameters Mean ± SD	Stage I (n = 6)	Stage II (n = 7)	Stage III (n = 19)	Pairwise comparisons p values	
				I–II	I–III
Hemoglobin [g/dL]	11.52 ± 1.68	12.76 ± 1.24	11.41 ± 1.1	0.205	0.976
Leukocyte [KμL]	7.17 ± 1.59	7.75 ± 2.10	11.25 ± 3.25	0.927	0.007*
Platelet [/mm^3]	261714 ± 66.81	237001 ± 47.42	262210 ± 74.11	0.796	1.000
MPV [ƒL]	10.12 ± 0.97	9.63 ± 1.34	9.67 ± 1.16	0.727	0.660
RDW	14.61 ± 2.20	14.16 ± 1.84	13.70 ± 1.27	0.873	0.421
NLR	3.1 ± 2.46	2.11 ± 0.93	5.01 ± 4.47	0.881	0.516
PLR	137.4 ± 25.17	113.9+24.22	136.7 ± 58.98	0.665	0.988

*Indicates statistically significant difference. Statistically significant ($p < 0.05$); SD — standard deviation; Stage I — invasion is limited to the mucosa; Stage II — invasion is limited to the muscular layer; Stage III — invasion to the subserosa or serosa; MPV — mean platelet volume; RDW — red cell distribution width; NLR — neutrophil/ /lymphocyte; PLR — platelet/lymphocyte; n — number of patients

Table 3. Initials serum levels of β-hCG accordance with the degree of infiltration into the tuba uterina

Depth of the trophoblastic invasion	n (%)	Initial β-hCG [mIU/mL] Mean ± SD (Min–Max)	p values
Stage I + II	13 (40.62%)	2276.45 ± 1654.91 (128–5720)	**0.02***
Stage III	19 (59.38%)	8015.38 ± 10746.96 (560–37170)	

*Indicates statistically significant difference. Statistically significant ($p < 0.05$). The Shapiro-Wilk test was used to determine whether the groups were normally distributed, and Kruskal Wallis test was performed; SD — standard deviation; Stage I — invasion is limited to the mucosa; Stage II — invasion is limited to the muscular layer; Stage III — invasion to the subserosa or serosa; n — number of patients

specificity, 71.4% positive predictive value, and 63.6% negative predictive value. SII score were also significantly higher in patients with stage III infiltration than in those with stages I or II ($p < 0.04$) (Tab. 4). The SII value that best predicted stage III trophoblastic infiltration, at 92.3% sensitivity and 63.1% specificity, was 792 (Fig. 4).

DISCUSSION

This study is the first attempt in literature to evaluate the association between SII score and tubal rupture. Our findings revealed that the SII score is highly associated with tubal invasion level. Moreover, we observed that the elevated SII values can be used as an additional marker for predicting rupture in ampullary tubal EP.

Adaptive changes in the immune system that occur during pregnancy are of great importance to both the mother and the fetus. However, any placental inflammation and invasion of cellular components in the intervillous space by various molecules or agents may result in adverse perinatal outcomes [12]. EP occurs when a fertilized egg is implanted

Table 4. Initials serum levels of Systemic Immunity-inflammation Index (SII) in accordance with the degree of infiltration into the tuba uterina

Depth of the trophoblastic invasion	n (%)	Initial SII Mean ± SD (Min–Max)	p values
Stage I + II	13 (40.62%)	618.38 ± 253.48 (248–1169)	0.04*
Stage III	19 (59.38%)	1176.14 ± 848.08 (310–3960)	

*Indicates statistically significant difference. Statistically significant ($p < 0.05$); SD — standard deviation; Stage I — invasion is limited to the mucosa; Stage II — invasion is limited to the muscular layer; Stage III — invasion to the subserosa or serosa; n — number of patients

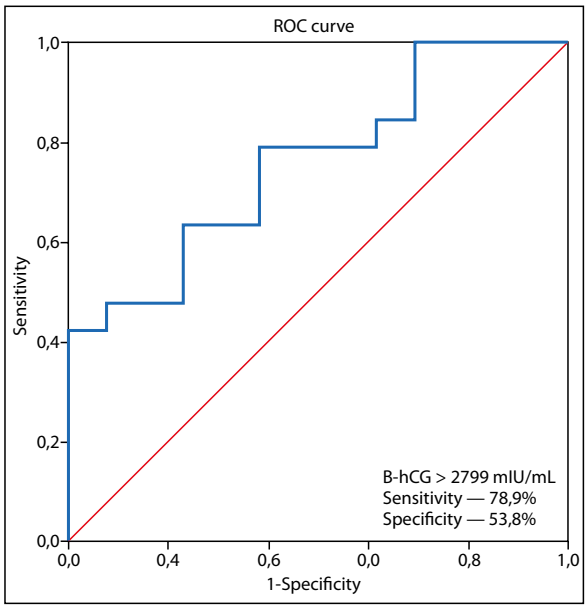

Figure 3. Receiver operating characteristic (ROC) curve correlating baseline values of β-hCG starting fallopian tube trophoblastic wall invasion in stage III

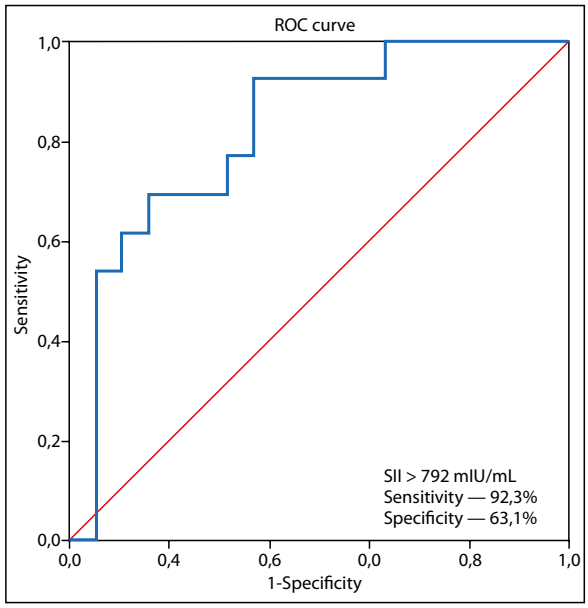

Figure 4. Receiver operating characteristic (ROC) curve correlating baseline values of Systemic Immunity-Inflammation Index (SII) starting fallopian tube trophoblastic wall invasion in stage III

anywhere other than in the endometrial cavity, the most common site being the fallopian tubes. Recent research has reported a link between high serum β-hCG levels and proportional increase in trophoblast and infiltration depth to the tuba uterine [9–13]. Darkhaneh et al. [13] also reported that the best cut-off points of serum β-hCG for predicting tubal rupture in EP was 1750 IU/mL (62% sensitivity, 73.6% specificity). Elito Jr. et al. [9] discovered that a β-hCG cut-off value of 2906 mIU/mL (85.7% sensitivity and 69.2% specificity) was associated with stage III invasion in a prospective study of 27 patients with EP. A serum β-hCG level of 2799 mIU/mL was found to be the most accurate indicator of stage III trophoblastic infiltration in the current study, which is similar to the 2906 mIU/mL cut-off point reported by Elito et al. [9]. Based on our findings, we propose that elevated β-hCG levels are strongly associated with serous tube involvement, that there may be an increased risk of rupture, and that surgical therapy may be required instead of drug therapy.

Cellular immune inflammatory indices such as the NLR and PLR, and SII have frequently been studied as disease indicators in clinical settings in the past decade [12, 14]. The efficacy of assessing maternal complete blood count parameters and cellular immune inflammatory indices to predict adverse obstetric outcomes has been the subject of several studies [8–12]. Studies have reported an increase in various inflammatory cytokines has been determined in both the implantation region and the systemic circulation in EP [15].

Turgut et al. [16] reported significantly higher leukocyte levels in the EP group without tube rupture compared to the control group in their study on the leukocyte levels in patients with EP. They also reported that there is no significant difference between the rupture and non-rupture cases in terms of mean platelet volume (MPV) values. Consistent with these results, in the current study, the increase in leukocyte counts in the stage III group compared to the stage I and II groups was statistically significant. As a matter of fact, our

results are in agreement with the study of Turgut et al. [16]. On the other hand, we observed no significant difference in terms of MPV values.

Tanacan et al. [8] demonstrated that the SII is a cost-effective and practical additional indicator for predicting adverse neonatal outcomes in pregnancies complicated by preterm premature membrane rupture. Furthermore, for low-risk pregnant women, a SII threshold value of 883.95 (10 9/L) (62.6% sensitivity, 62% specificity) was reported in a study involving patients with a clinically low risk of miscarriage. That research showed that high SII values in pregnancy can be used to predict miscarriage in pregnant women at risk of the threatened abortion [12]. Our findings showed that the SII value correlated with the depth of trophoblasts invading the tuba uterina wall. In our cohort, the SII value of stage III cases was higher than that of stage I and II cases. Based on this data, we proposed that a high SII score might be used as a marker of advanced infiltration. Therefore, the evaluation of the SII value can be a guide in determining the treatment modality.

Despite the small sample size, the findings suggested that β-hCG levels and SII scores are highly associated with the depth of trophoblasts invading the tuba uterina wall Low β-hCG levels and a low SII score can be interpreted as superficial (mucosal) trophoblast infiltration in the tubal wall, indicating that the patient is more likely to benefit from medical treatment. High β-hCG levels and SII scores, on the other hand, are risk factors for tubal rupture; therefore, surgery should be the first option in treatment.

CONCLUSIONS

Our findings indicated that serum β-hCG and SII score were highly associated with the depth of trophoblast infiltration into the tube wall. The SII is a cost-effective parameter for predicting the risk of tubal rupture in ampullary EPs and may be useful in guiding the surgical decision, particularly in settings in which resources are limited.

Declarations

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. All authors read and approved the manuscript for publication.

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Conflict of interest

The authors declare no conflicts of interests. This work complies with ethical standards and the Helsinki Declaration.

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