Elevated serum YKL-40 levels as a diagnostic and prognostic marker in the placenta accreta spectrum

Plasenta invazyon anomalilerinin tanısı ve prognozunda artmış serum YKL-40 seviyeleri

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Abstract

Objective: Placenta accreta spectrum (PAS) is an important problem with increasing cesarean section (CS) rates recently. There is still no serum marker for the diagnosis. We determined whether serum YKL-40 levels can be used in the diagnosis and prognosis of PAS.

Materials and Methods: The study was conducted with 50 patients with a PAS diagnosis, 27 individuals without PAS, and 33 normal pregnant women. The operations (CS + placental bed suture, CS + excision of the lower segment, CS-hysterectomy) and for individuals who had the excision of the lower segment /CS-hysterectomy, the histopathological diagnoses (accreta, increta, percreta) were recorded. Serum YKL-40 levels were analyzed.

Results: The individuals with PAS possessed significantly greater serum YKL-40 grades (p=0.001). The surgical interventions included 4 CS + excision of the lower segment, 9 CS + placental bed sutures, and 37 CS-hysterectomy. The histopathological outcomes of the individuals who had the excision of the lower segment, CS-hysterectomy and diagnosed 6, 9, and 26 patients with accreta, increta, and percreta, respectively. The accreta, increta, and percreta groups showed statistically significant different serum YKL-40 grades (p=0.001). The receiver operating characteristic analysis was performed to discriminate the cut-off serum YKL-40 level as 32.81 ng/mL with a sensitivity of 66% and specificity of 70.37%. The positive and negative predictive values of YKL-40 in the indicator of PAS were 80.5% and 52.8%, respectively.

Conclusion: Elevated serum YKL-40 grades were correlated with the diagnosis and severity of PAS. If our findings are corroborated and elaborated by larger patient series, the YKL-40 levels should be used along with ultrasonography to construct a model identical to that used in aneuploidy screening.

Keywords: Abnormal placental invasion, cesarean section, placenta accreta spectrum, ultrasonography, YKL-40

Öz

Amaç: Plasenta akreata spektrumu (PAS) artan sezaryen oranlarıyla son yıllarda önemli bir sorun haline gelmiştir. Ancak hastalığın tanısında kullanılabilecek bir serum markeri hala yoktur. Çalışmada serum YKL-40 seviyelerinin, hastalığın tanısı ve prognozunda kullanılabilecek bir marker olup olmadığını ortaya koymak amaçlanmıştır.

Gereç ve Yöntemler: Çalışmaya transabdominal renkli Doppler ultrasonografide (TA-RDS) PAS öngörüsü olan 50 hasta ile PAS olmayıp eski sezaryen öyküsü bulunan 27 kontrol hastası ve 33 normal gebe dahil edildi. Hastaların operasyonlarında ne yapıldığı (sezeryan + servikal yatak suturu, sezeryan + alt segment eksizyon, sezeryan-histerektomi) ve alt segment eksizyon/sezeryan-histerektomi yapılan hastaların histopatolojik bulguları (accreta, increta, percreta) kayıt altına alındı. YKL-40 seviyeleri enzim linked immünosorbent assay yöntemi ile analiz edildi. PAS'nin öngörüsünde serum YKL-40 seviyelerinin optimal cut-off değerini belirlemek için alıcı işletim karakteristiği (ROC) testi kullanıldı.

Bulgular: Hasta grubunun serum YKL-40 seviyesi, diğer gruplara göre anlamlı derecede yüksekti (p=0,001). Elli hastanın operasyonlarında, 4'üne (%8) sezaryen + alt segment eksizyon, 9'una (%18) sezaryen + servikal yatak süturu, 37'sine (%74) sezaryen-histerektomi uygulandı. Alt segment eksizyon ve sezaryen histerektomi uygulanan hastaların histopatolojik sonuçları değerlendirildiğinde 6 (%14,6) hasta accreta, 9 (%22) hasta increta ve 26 (%63,4) hasta percreta tanısı aldı. Accreta, increta ve percreta grupları arasında serum YKL-40 seviyeleri bakımından anlamlı farklılık izlendi (p=0,001). ROC analizinde,

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%66 duyarlılık ve %70,37 özgüllük ile serum YKL-40 seviyeleri için cut-off değer 32,81 ng/mL olarak bulundu. YKL-40'ın PAS tahmininde pozitif ve negatif prediktif değerleri sırasıyla %80,5 ve %52,8 idi.

Sonuç: Artmış serum YKL-40 seviyeleri PAS'nin varlığı ve derecesi ile ilişkilidir. Bulgularımız daha geniş hasta serileri tarafından desteklenir ve detaylandırılırsa, anöploidi taramasında kullanılana benzer bir model oluşturmak için, YKL-40 seviyeleri ultrasonografi ile birlikte kullanılabilecek bir marker olabilir.

Anahtar Kelimeler: Anormal plasental invazyon, sezaryen section, plasenta acreata spektrum, ultrasonografi, YKL-40

Introduction

Placenta accreta spectrum (PAS), which is described as an unusual trophoblast violation of the myometrium by the placenta, is closely linked to massive obstetric hemorrhage and postpartum hysterectomy[1]. The incidence of PAS has increased due to the rise in cesarean section (CS) rates in recent decades[2]. Histologically, the PAS is allocated according to the harshness of myometrial invasion by extravillous trophoblasts (EVT). In the placenta accreta, there is the partial attachment of the myometrium without invading it by placental villi. In the placenta increta, chorionic villi completely infect the myometrium. While in the placenta percreta, the villi have advanced beyond the myometrium into the uterus serosa and surrounding tissues[3]. The abnormal adherence of EVT in PAS can be caused by an absence of decidua basalis, excessive invasion by EVT, or a combination of these two factors[4]. This assumption is supported by the fact that 80% of PAS patients report a history of CS, myomectomy, and/or curettage operations[5].

Studies have reported various autocrine and paracrine regulators of EVT invasion that include growth factors, matrix metalloproteases, chemokines, cytokines, and adhesion molecules[6]. The YKL-40 (Human Chitinase-3-like protein 1), which is also recognized as the human cartilage glycoprotein 39, acts as a chemoattractant. It is an inflammatory glycoprotein that supports vascular endothelial cells and tubulogenesis and migration[7]. YKL-40 is also linked to the extracellular tissue remodeling, proliferation and differentiation of malignant cells, neovascularization, stimulation of cancer-associated fibroblasts, and inhibition of cancer cell apoptosis[8]. Elevated serum levels are linked to problems in the extracellular matrix and angiogenesis[9].

YKL-40 is secreted predominantly by neutrophils, macrophages, endothelial, stem, and cancer cells[4]. Its levels increase in the presence of various diseases, including cancer, osteoarthritis, cardiovascular diseases, neurological diseases, infections, chronic obstructive pulmonary disease, asthma and preeclampsia, gestational diabetes, and cholestasis of pregnancy[8]. However, the correlation between YKL-40 and PAS is not known.

The contribution of YKL-40 to trophoblast invasion has been investigated by inspecting hysterectomy specimens of PAS patients[7]. However, according to our literature review, there isn't any study that has examined the serum levels of YKL-40 in PAS and attempted to correlate these parameters with the histopathological findings.

Based on the assumption that YKL-40 contributes to excessive EVT invasion, this study determines the serum levels of YKL-40 in the individuals suspected of having PAS and to investigate whether the YKL-40 can be used as a prognostic and diagnostic marker of PAS by correlating these levels with histopathological findings (accreta, increta, and percreta).

Materials and Methods

The patients with a diagnosis of PAS in the Southeast region of our country were referred to our hospital because our hospital is the tertiary referral center. Our study included 50 patients who applied to Gaziantep University, Medical Faculty Obstetrics and Gynecology Polyclinic between the dates of January 2019 and September 2019 and had the PAS in ultrasonography.

Between the dates of January and September 2019, 128 total placenta previa cases were detected in our clinic. In 53 cases, PAS was detected on trans-abdominal-ultrasonography (TA-USG), whereas PAS was not observed in 75 patients. Three of the patients with PAS refused to participate in the study. So, the study included 50 total placenta previa patients in the 3rd trimester of pregnancy with a previous history of CS and who were detected to have PAS on TA-USG in the current pregnancy, 27 total placenta previa patients who had a previous history of CS but did not have PAS in the current pregnancy, and as a control group, 33 normal pregnant women with a history of previous CS. All groups were matched in terms of age, body mass index (BMI), and gestational week.

Pregnant patients who had gestational diabetes, systemic diseases, gestational HT, multiple pregnancies, preeclampsia, low-lying placenta previa, chromosomal or structural fetal anomalies, and pregnant patients who smoked were excluded from the study. This study was conducted in line with the guidelines stated in the Helsinki Declaration, and the approval was obtained from the Clinical Research Ethics Committee of the Faculty of Medicine (approval number: 2019/317).

TA-USG and Doppler USG examinations of the experimental and control groups' patients were performed in the department of Gynecology and Obstetrics by a single experienced physician using a Voluson E8® (GE Healthcare) device. Placenta previa totalis is diagnosed when the placenta stretches directly over the internal cervical os[10]. Using gray-scale/color Doppler TA-USG, we investigated the following items for PAS; loss/unregularity of the echolucent space between the placenta and uterus (clear zone), disruption of the hyperechoic area between the uterine serosa and bladder, and the presence of turbulent placental lacunae[11].

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All patients who participated in the study signed a consent form. After fasting for 12 h, venous blood samples were collected from all participants. After coagulation, the samples were centrifuged to obtain serum and kept at -80 °C until analysis. Serum YKL-40 levels were calculated using commercially available enzyme-linked immunosorbent assay (ELISA) kits (Rel Assay DC, Gaziantep, Turkey). The Serum YKL-40 levels were determined as ng/mL. The number of pregnancies and births, age, and previous CSs, gestational week, BMI, the presence of CS-hysterectomy in the current pregnancy; if present, histopathological diagnosis (accreta, increta, and percreta), and the serum YKL-40 levels were recorded for all pregnant participants.

Statistical Analysis

In terms of YKL-40 levels between the groups, a large effect size level (Cohen d=1), the required minimum number of participants in each group was determined as 27 for the expected difference to be statistically significant (α=0.05, 1-β=0.80). Power analysis was done in G-power 3.1.9.2 package program.

The quantitative variables were checked for normal distribution using the Shapiro-Wilk test. ANOVA and LSD tests were used to compare variables with a normal distribution in the three groups, while Dunn and Kruskal-Wallis tests were used for the variables presenting non-normal distributions. The analysis of the receiver operating characteristic (ROC) curve was performed to calculate a cut-off rate for the YKL-40 levels. Statistical analysis were carried out with using the SPSS 22.0 for Windows and Medcalc 17.5.5, and a p-value<0.05 was determined statistically significant.

Results

The groups were not different in terms of gravida, age, parity, the number of previous CSs, gestational week, and BMI (Table 1).

The Mean YKL-40 was determined as 34.07±9.68 ng/mL for the PAS group, 28.4±6.93 ng/mL for those without PAS, and 15.76±2.57 ng/mL for the normal pregnancy group. The mean YKL-40 of the PAS group was significantly greater than that of the other two groups, (p=0.001).

Among the surgical interventions performed on the 50 patients who were detected to have PAS on TA-USG included, 4 of them had CS+excision of the lower segment operations (8%), 9 of them had CS+placental bed suture operations (18%), and 37 of them had CS-hysterectomy operations (74%). Since the placenta was removed in 9 patients and invasion was detected only in the cervical canal, the operation was terminated with CS+placental bed suture, and a Bakri balloon was placed when necessary. The placental pathologies of these patients were "normal." The mean YKL-40 value of 9 patients who were detected to have PAS on TA-USG and only CS+placental bed suture was performed in the operation was 18.75±3.86 ng/mL. The histopathological outcomes of the participants who underwent excision of the lower segment and CS-hysterectomy were as 6 individuals (14.6%) with accreta, 9 individuals (22%) with increta, and 26 (64.3%) with percreta. The accreta, increta, and percreta groups presented statistically significant different serum levels of the YKL-40 (p=0.001).

The YKL-40 levels were greater in the percreta group than in the increta and accreta groups, and it was greater in the increta group than in the accreta group, significantly (Table 2). YKL-40 values of the patients who had CS + placental bed suture were significantly lower than the accreta, increta and percreta groups

Table 1. Main clinical features of the groups

Variables	Patients with API group (n=50)	Patients without API group (n=27)	Control group (n=33)	p
Age	33.14±4.41	33.56±5.85	33.03±2.05	0.885
Gravida	4.88±1.53	4.41±1.25	4.7±0.64	0.306
Parity	3.38±1.14	3.11±1.12	3.61±0.66	0.066
Number of previous CS	3.12±0.92	3.11±0.93	3.03±0.77	0.988
Gestational week	33.94±1.95	33.89±2.65	34.18±1.21	0.741
BMI (kg/m²)	27.45±2.35	27.86±2.56	27.52±1.12	0.744

API: Abnormal placental invasion, BMI: Body mass index

Table 2. The comparison of YKL-40 rates between the accreta, increta, and percreta subgroups

	Accreta (n=6)	Increta (n=9)	Percreta (n=26)	p
YKL-40 (ng/mL)	27.23±3.32	35.09±4.29	40.6±5.5	0.005[a] 0.001[b] 0.007[c]

[a]: Increta versus accrete, [b]: Percreta versus accrete, [c]: Percreta versus increta

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(CS versus accreta, CS versus increta, and CS versus percreta; p=0.002, p=0.001, and p=0.001, respectively). This group was considered the group that TA-USG was a false positive.

The analysis of the ROC curve was performed to calculate a cut-off serum YKL-40 level for indicating PAS. The place under the ROC curve was calculated as 0.68 (95% confidence interval, 0.57-0.98; p=0.002). The cut-off value for YKL-40 was calculated as 32.81 ng/mL with a sensitivity of 66% and specificity of 70.37% (Figure 1). The positive and negative predictive values of YKL-40 in the indication of PAS were 80.5% and 52.8%, respectively.

Discussion

To our knowledge, this study is the first that has analyzed the serum YKL-40 levels in PAS. In this study, we found elevated YKL-40 levels in PAS, which presented a significant increase from accreta to increta, and increta to percreta. Another significant outcome of our study is that the YKL-40 could be a useful prognostic and diagnostic marker for PAS cases with a good level of sensitivity (66%) and specificity (70.37%).

PAS is a condition that can cause both fetal and maternal mortality and morbidity. Maternal complications are generally linked to the difficulty of the operation and bleeding, while neonatal and fatal complications are connected to prematurity that emerges from the operations performed due to bleeding[12]. Therefore, identifying a preoperative diagnostic and prognostic method that could confirm the risk of PAS is quite important. In the antepartum period, the TA-USG is the primary method for the confirmation of placental abnormalities with a high level of sensitivity (85.7%) and a high level of specificity (88.6%)[13]. Some serum markers were also investigated in PAS, and the reliability of the variable was determined depending on the gestational conditions[14]. At present, a sensitive serum marker for the invasive placement is still unclear.
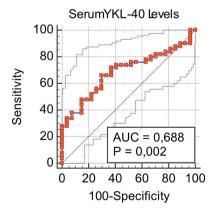

Figure 1. ROC curve of the indicator value of serum YKL-40 rates in API. ROC curve to evaluate the diagnostic value of YKL-40 in PAS. The YKL-40 rates of participants with and without PAS were utilized to create a ROC curve and affiliated values of specificity, sensitivity, and AUC were calculagted.

ROC: Receiver-operating characteristics, AUC: Area under the curve

As our hospital is a tertiary center, it provides care for the PAS cases not only in our city but also in surrounding cities. When treating patients with suspected invasion, preparing for transfusion requirements, conducting the operation under elective conditions, and arranging the surgical team (comprised of a neonatologist, perinatologist, and if needed, a gyneco-oncologist and urologist) are essential to help the family psychologically prepare themselves for a difficult operation. Although ultrasonography is an effective method for showing abnormal placental invasion, it does not provide sufficient information about the depth of invasion. Therefore, it is difficult to determine the abnormal invasion of the accreta, increta, and percreta groups by USG[15].

A serum biomarker that would support the diagnosis of PAS can facilitate us without the need for more expensive magnetic resonance imaging (MRI) method in the preoperative period. In this regard, a marker that would complement ultrasonography in the preoperative period may increase diagnostic accuracy and save the lives of both the fetus and mother. If such a marker is used and the pre-diagnosis of PAS based on TA-USG is confirmed by a serum biomarker, individuals can be referred to tertiary centers for management, and they can be followed up at more frequent intervals.

In our study, there were 9 patients who were detected to have PAS on ultrasonography in the preoperative period, but who did not reveal PAS during the operation. These patients were evaluated as those in which ultrasonography was "false positive." The mean YKL-40 level of these patients was lower than those of both the accreta, increta, and percreta groups (18.75±3.86 ng/mL vs 27.23±3.32; 35.09±4.29; 40.6±5, 5 ng/mL) and the total placenta previa group without PAS (18.75±3.86 ng/mL vs 28.4±6.93 ng/mL), but the mean YKL-40 level of these patients was greater than the normal pregnancy group (18.75±3.86 ng/mL vs 15.76±2.57 ng/mL). This suggests that the YKL-40, which can be used along with ultrasonography in the preoperative period, can help us with the depth of invasion.

YKL-40 plays a crucial part in the restructuring of the extracellular matrix, the activation of the natural immune system, angiogenesis, the growth, differentiation, and anti-apoptosis of tumor cells[8].

Typically, the serum YKL-40 levels increase between the 12th and 20th gestational week, maintain a steady level between the 20th and 25th week, and decrease after the 32nd week. It is not acknowledged whether this increase and the subsequent decrease present the implantation and placental development processes- both processes require angiogenesis and tissue remodeling[16]. Certain studies have implicated the YKL-40 as a potential tumor marker. To this date, *in vitro* studies have determined the YKL-40 overexpression in various tumors, including osteosarcoma, prostate cancer, glioma, colon cancer, and endometrial cancer[8].

We designed this study based on the idea that the YKL-40 levels could be increased in PAS as the abnormal EVT invasion can be

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considered a tumorous formation. In a study conducted by Guo et al.[8], the serum YKL-40 rates were determined to be greater in patients with leiomyoma than in the control group, and a positive correlation was determined between the YKL-40 grade and the myoma weight. YKL-40 was revealed to be a useful indicator for detecting leiomyoma with a sensitivity of 82% and specificity of 91%. Similarly, this study found higher YKL-40 grades in the individuals who were detected to have PAS on TA-USG compared with those who were not. The YKL-40 grades were determined to be elevated from the accreta to the percreta. YKL-40 rates exceeding 32.8 ng/mL were associated with an increased PAS risk, with 66% sensitivity and 70.37% specificity.

Although the role of YKL-40 is not obvious, its overexpression has been linked to the signaling pathways of mitogenic activity[7]. Many studies have explored the effects of YKL-40 on extracellular matrix remodeling and the invasion of cancer cells[7]. Accordingly, it is plausible that the YKL-40 affects PAS due to the inhibition of excessive EVT invasion and EVT apoptosis through the extracellular matrix remodeling.

The YKL-40 has also been shown to be related to endothelial dysfunction[17]. Seol et al.[18], conducted a study that determined higher YKL-40 rates in the individuals with preeclampsia and identified a correlation with the severity of the disease. In the cases of placenta accreta and placenta previa without PAS, increased YKL-40 grades may be expected as the scar site undergoes defective maternal vascular remodeling[19]. This hypothesis is corroborated by the findings of our study that indicated increased YKL-40 levels in the PAS group.

A study by Gozukara et al.[7] examined the tissue expression levels of YKL-40 in hysterectomy specimens of the PAS patients and determined the strongest expression in the percreta cases, reported that the YKL-40 grades were correlated with the EVT invasion. Differently from the cited study, we studied the serum rates of YKL-40 in the individuals with PAS and determined that the patients with invasion had elevated levels, which were correlated with the degree of invasion. Correlated with the results of the study by Gozukara et al.[7], which revealed the greatest YKL-40 possession in the percreta group, our study determined the highest YKL-40 rates in the percreta group.

The study showed for the first time that the PAS is affiliated with increased YKL-40 rates and that across the accreta, increta, percreta groups, these levels were greater in the percreta group than in the increta and accreta groups, and greater in the increta group than in the accreta group, significantly. The lower YKL-40 levels of patients who were detected to have PAS on ultrasonography but without PAS during the operation and had CS + placental bed suture, compared to the accreta, increta, and percreta groups supported the increase of YKL-40 rates with the possession of invasion. In these patients, the prediction of PAS on ultrasonography is the false positivity of USG.

Study Limitations

The limitation of this study is that the number of patients who could have been included in each group (accreta, increta, and percreta) was small and the YKL-40 rates were measured only in the third trimester. Our study is a reference study that is the first to divide patients into accreta, increta, and percreta groups according to the serum marker levels and to correlate these findings with the pathology findings.

In this study, it was aimed to present whether the YKL-40 levels would provide a cut-off value between the accreta, increta, and percreata groups that support our ultrasonographic findings. Thus, we planned to determine which disease group (accreta, increta, percreta) the patient would fall in the preoperative period in patients with PAS detected by the ultrasonography and serum YKL-40 level, without the need for an expensive diagnostic tool such as MRI. The fact that the YKL-40 rates in the PAS group were significantly greater than the other 2 groups (normal pregnant and placenta previa without PAS) will guide new studies in terms of using this serum marker as an additional diagnostic tool to ultrasonography in the diagnosis of PAS.

Conclusion

If the results of our study are corroborated by the studies that possess a larger number of participants for each subgroup (accreta, increta, and percreta), it would be possible to confirm both the pathophysiological effects and the prognostic and diagnostic utility of YKL-40 levels in PAS. By confirming the YKL-40 and ultrasonography, a model that is similar to that used for screening the aneuploidy [Alpha-Fetoprotein+USG] may be considered for the PAS. Nonetheless, the assistance of that stands as an unknown feature until greater prospective data from the larger populations are available.

In the cases of recurrent CS, a study with larger samples can be organized on the correlation between the YKL-40 grades and the development of PAS in the early second trimester or the late first trimester. Thus, the YKL-40 grades should become a marker that could be used in the prediction of PAS before the ultrasonographic findings occur.

Ethics

Ethics Committee Approval: This study was conducted in line with the guidelines stated in the Helsinki Declaration, and the approval was obtained from the Clinical Research Ethics Committee of the Faculty of Medicine (approval number: 2019/317).

Informed Consent: All patients who participated in the study signed a consent form.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: N.B.T., D.B., Design: N.B.T., Data Collection or Processing: N.B.T., İ.T., Analysis or Interpretation: N.B.T., İ.T., Literature Search: D.B., Writing: N.B.T.

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