

The Role of YKL-40 in the Diagnosis of Placenta Accreta Spectrum in a Group of Iraqi Patients

Najmah M. Meran*¹  , Zina E. Mohammed²  

¹Department of Obstetrics and Gynecology, College of Medicine, University of Baghdad, Baghdad, Iraq.

²Department of Obstetrics and Gynecology, Baghdad Teaching Hospital, Medical City Complex, Ministry of Health, Baghdad, Iraq.



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Abstract

Background: As the number of caesarean deliveries has escalated over the last 50 years, Placenta Accreta Spectrum is now emerging as a more frequent pregnancy-related issue. The incidence of this problem is increasing, with recent estimates indicating an approximate 1/333 to 1/533 deliveries. Recent studies reveal that YKL-40 (also known as Chitinase-3-like protein 1 which is a secreted glycoprotein that is approximately 40kDa in size) may be involved in angiogenesis, cell proliferation and differentiation as well as extracellular matrix remodeling, and other inflammatory processes.

Objectives: To evaluate the association between maternal serum YKL-40 levels and the severity of Placenta Accreta Spectrum.

Methods: A case - control study was conducted in the Department of Obstetrics and Gynecology at Baghdad Teaching Hospital, Baghdad, from June 1, 2023, to June 1, 2024. It included 97 pregnant women with singleton pregnancy in the third trimester, having a diagnosis of Placenta Accreta Spectrum (37 patients), and those with normally sited placenta admitted for delivery either by vaginal or caesarean section (60 controls). The serum YKL40 biomarker was investigated in both groups.

Results: The mean level of the YKL-40 was significantly higher in patients diagnosed with placenta accreta spectrum than in those with a normal placenta. As the cut-off point for the YKL-40 is 112.68 pg/ml, a YKL-40 level > 112.68 pg/ml was associated with placenta accreta spectrum.

Conclusion: Serum YKL-40 appears to be a promising biomarker associated with the presence and clinical severity of Placenta Accreta Spectrum in the third trimester. While its role as a primary diagnostic tool is limited by the availability of imaging techniques at this stage of pregnancy, it shows a significant correlation with the depth of placental invasion.

Keywords: Biomarker; Morbidly Adherent Placenta; Placenta Accreta Spectrum; Placenta Previa; YKL-40.

Introduction

Placenta Accreta Spectrum (PAS), a condition formerly considered rare, is becoming increasingly common in current obstetrical practice. This condition occurs when improper implantation at the basal plate prevents the placenta from separating from the uterine wall, causing severe bleeding, necessitating blood transfusions, resulting in multiorgan failure, a morbid hysterectomy, and even death (1).

Even if the discrepancy in maternal mortality and morbidity between the industrialized and developing countries has reduced, much effort is still required to explain these disparities. This aberrant placental implantation and the problems that ensue have resulted from several different causes. Sustained and sincere efforts have been made to determine the risk factors for aberrant placentation during pregnancy, as well as ways to avoid and treat them (2). The failure of the placenta to separate at delivery is the chief characteristic of PAS,

which includes placenta accreta, increta, and percreta. Patients face considerable risk of perinatal and maternal morbidity and mortality.

Optimal care for women with PAS should be based on recent information that permits the women and their caregivers to prepare for the complications that may accompany the delivery (3).

Recently, FIGO (International Federation of Gynaecology and Obstetrics) proposed a pathologic grading classification, which has replaced the traditional categorical nomenclature (placenta accreta, increta, and percreta) with the standardised clinical classification and new terminology of the Placenta Accreta Spectrum (PAS), encompassing all grades of abnormal placentation(4).

Stem cells, inflammatory cells, and cancer cells all manufacture the 40-kDa glycoprotein known as YKL-40. This most likely plays a role in inflammation, the prevention of apoptosis, stimulation of angiogenesis,

*Corresponding Author: najmah@comed.uobaghdad.edu.iq

cell proliferation and differentiation, and the regulation of extracellular tissue remodelling(5),(6) .

The current study aims to evaluate the association between maternal serum YKL-40 levels and the severity of Placenta Accreta Spectrum.

Patients and Methods

A case-control study was conducted in the Department of Obstetrics and Gynecology at Baghdad Teaching Hospital, Medical City Complex, Baghdad, Iraq from June 1, 2023 until June 1, 2024. The study included 97 pregnant women with singleton pregnancy in the third trimester, either admitted to the obstetric ward of the Baghdad Teaching Hospital, with a diagnosis of PAS, or with normally sited placenta coming to the hospital for delivery, either vaginally or by caesarean section. The purpose of the study was explained to them, and verbal consent was taken.

They were segregated into two groups:

1. **PAS group:** Included 37 pregnant women diagnosed with abnormally invasive placenta.
2. **Control group:** Included 60 healthy, pregnant women with no complications, having normal placental location matched with the other groups for maternal age and gestational age at the time of delivery.

Inclusion criteria: Woman age ≥ 18 years, with a gestational age ≥ 28 weeks and a single viable fetus.

Exclusion criteria: Multiple pregnancy, gross fetal abnormalities, hypertension, diabetes mellitus, renal disease, thyroid dysfunction, bacterial infections, asthma, and women with cervical cerclage, D&C, and myomectomy.

Full history was taken from all the women, including age, obstetrical history, including gestational age (GA), parity, last menstrual period (LMP) and prior medical history. History of the current pregnancy included Antepartum Haemorrhage (APH) and past obstetrical history with special attention paid to uterine surgery (number of previous C/S or manual removal of the placenta). At the time of presentation, the gestational age was determined using the first day of LMP and verified by an early abdominal ultrasound scan.

General examination, including vital signs, an obstetric abdominal examination was done, specifically to note the fundal height, uterine contractions and fetal heart sounds. A 10 ml blood sample was drawn from each woman for routine investigations (blood group, Rh typing, blood sugar, full blood count, liver function tests, renal function tests and coagulation profile were done using 5 ml of the sample, while the serum YKL-40 level was tested using the remaining 5 ml, which was centrifuged for 15 minutes at $1000\times g$ at $2-8^{\circ}C$ after being allowed to clot for two hours. The supernatants were stored at a temperature of $-20^{\circ}C$ or $-80^{\circ}C$ for later use, or they had to be used at once for assay testing. The Sandwich-ELISA principle was applied to measure the biomarker. The detection range: 10 to 320 pg/ml.

A skilled ultra-sonographer at the Baghdad Teaching Hospital conducted the Doppler ultrasound tests. Confirmation of PAS was done through histopathological examination of the resected placenta by a professional pathologist at the Teaching Laboratories of Medical City Hospital.

Ethical considerations: Before any data was collected, each patient gave her verbal consent, and the data was anonymized. Identification codes took the place of names. All data used were kept private on a password-protected laptop. The Baghdad Teaching Hospital's Department of Obstetrics and Gynecology gave its approval under code number (55) on April 17, 2023.

Statistical analysis: Version 26 of the Statistical Package for Social Sciences (SPSS) was used to analyze the data. The information is displayed as means, and standard deviations. Percentages and frequencies were used to display categorical data and tested using the Chi-square test. Differences between the two group means were compared using the independent sample t-test. A P-value of less than 0.05 was regarded as significant. The function of serum YKL40 as a biomarker for abnormally adherent placenta was assessed using ROC analysis.

Results

Among cases of PAS, 26 (70.3%) were diagnosed with placenta accreta, 7(18.9%) were diagnosed with placenta increta, and 4 (10.8%) were diagnosed with placenta percreta; as shown in (Table 1).

Table 1: Distribution of (PAS) cases group according to diagnosis.

PAS Classification	Number of Cases (N=37)	Percentage (%)
Placenta Accreta	26	70.3%
Placenta Increta	7	18.9%
Placenta Percreta	4	10.8%

Table 2 summarizes the demographic and clinical profiles of the study participants. No statistically significant associations were observed between the cases and controls regarding maternal age ($P = 0.427$) indicating that the two

groups were well matched for this parameter. However, significant clinical disparities were noted; the cases group exhibited significantly higher parity (4.1 ± 1.50 vs. 2.2 ± 1.10 , $P < 0.001$) and a higher frequency of previous cesarean sections (3.2 ± 1.70 vs. 1.4 ± 0.70 , $P < 0.001$). Furthermore, gestational age at delivery was significantly lower in the cases group compared to the control group (34.6 ± 4.60 vs. 37.1 ± 2.40 weeks, $P < 0.001$), reflecting the clinical complications associated with these cases.

Table 2: Demographic and clinical characteristics of the study groups

Variables	Groups: No (%)		Total: No (%) N=97	P- Value
	Cases (N=37)	Controls (N=60)		
Maternal age (years)				
Mean ± SD	30.3 ± 4.10	30.8 ± 6.40		0.654
<25	7 (18.9%)	18 (30.0%)	25 (25.8%)	0.427
25 – 34	16 (43.2%)	20 (33.3%)	36 (37.1%)	
≥ 35	14 (37.8%)	22 (36.7%)	36 (37.1%)	
Gestational age(week)				
Mean ± SD	34.6 ± 4.60	37.1 ± 2.40		<0.001
Preterm	30 (81.1%)	16 (26.7%)	46 (47.4%)	<0.001
Term	7(18.9%)	44 (73.3%)	51(52.6%)	
Mode of delivery				
VD	0 (00.0%)	36(60.0%)	36(37.1)	<0.001
C/S	37(100.0%)	24(40.0%)	61(62.9)	
Parity				
Mean ± SD	4.1 ± 1.50	2.2 ± 1.10		<0.001
Primigravida	0(0.0%)	16(26.7%)	16(16.5%)	<0.001
Para 1	6(16.2%)	16(26.7%)	22(22.7%)	
Multiparous	31(83.8%)	28(46.7%)	59(60.8%)	
No. of previous C/S				
Mean ± SD	3.2 ± 1.70	1.4 ±0.70		<0.001
None	2(5.4%)	24(40.0%)	26(26.8%)	<0.001
1-3	19(51.4%)	30(50.0%)	49(50.5%)	
> 3	16(43.2%)	6(10.0%)	22(22.7%)	

The mean YKL40 level was significantly greater in cases (195.0 ± 48.50 pg/ml) than the controls (66.2 ± 10.50 pg/ml) (P= <0.001).

Receiver operating characteristic (ROC) curve analysis was conducted for YKL40 levels in relation to abnormal placentation. The area under the curve (AUC = 97.2%) 95% confidence interval: (92.5% – 99.8%) indicates a significant association between higher levels of YKL40 and the presence of PAS. At a cut-off value

of 112.68 pg/ml, the marker shows a strong correlation with diagnosed cases, with 94.6% sensitivity (95% confidence interval 81.8% – 99.3%) and 100% specificity (95% confidence interval 94%-100%) in identifying patients within the disease spectrum, (Figure 1 and Table 3).

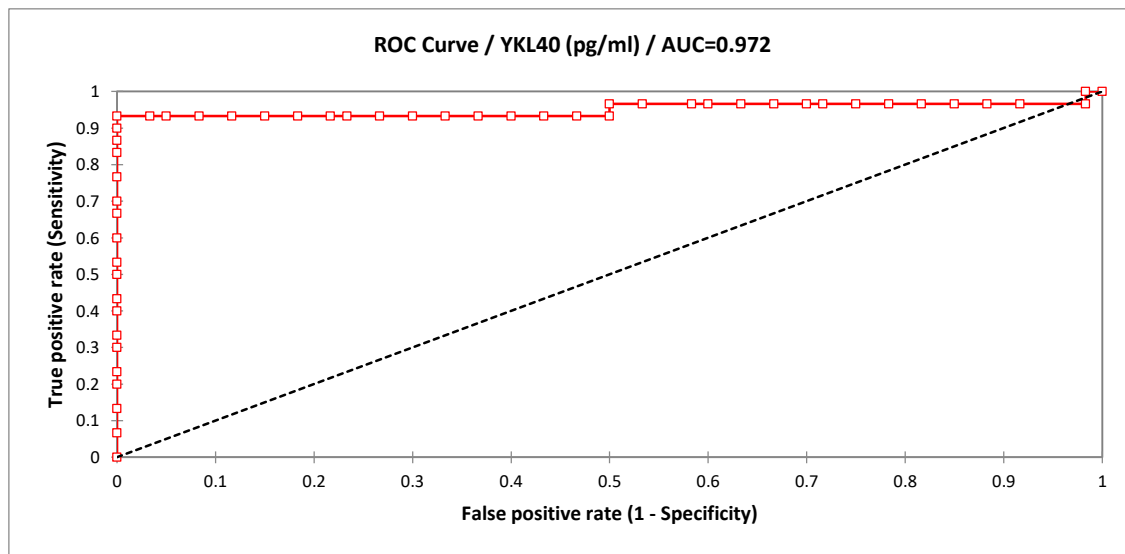


Figure 1: ROC curve analysis demonstrating the association between serum YKL-40 levels and PAS severity

Table 3: Diagnostic Performance of Serum YKL-40 in diagnosing PAS

Parameter	Value	95% Confidence interval
Cut-off point	>112.68 pg/ml	-
AUC	97.2%	92.5% – 99.8%
Sensitivity	94.6%	81.8% – 99.3%
Specificity	100 %	94%-100%
PPV	100%	94%-100%
NPV	96.8%	84.5% – 97.7%
accuracy	97.9%	91.6% – 99.1%

Moderate negative correlation found between GA and level of YKL-40. This suggests that higher levels of this protein are associated with earlier deliveries.

Moderate positive correlation between YKL-40 and number of previous CS. This indicates that as the number of previous surgical scars (C-sections) increases, the level of YKL-40 also increases. This

could be due to the inflammatory response associated with uterine scarring. The correlation between maternal age and YKL-4 is negligible. Since the p-value is 0.812, the result is not statistically significant. This means that the mother's age has no real impact on the levels of YKL-40, (Table 4).

Table 4: Correlation between YKL-40 and clinical characteristics in both study groups (N=97)

Characteristic	Correlation Coefficient (r)	P-Value	Interpretation
Gestational Age (weeks)	-0.432	< 0.001	Moderate Negative: Higher YKL-40 levels correlate with lower GA (preterm birth).
No. of previous C/S	+0.485	< 0.001	Moderate Positive: YKL-40 increases as the number of surgical scars increases.
Maternal Age	-0.024	0.812	Negligible: No correlation; age does not affect YKL-40 levels.

Within the PAS group, higher levels of YKL-40 are significantly correlated with earlier delivery (lower gestational age), ($r = -0.462$, $P = 0.004$). Strong correlation between YKL-40 and number of previous

CS ($r = +0.518$, $P = 0.001$). There is no statistically significant correlation between the maternal age and their YKL-40 levels ($r = +0.084$, $P = 0.621$), (Table 5).

Table 5: Correlation between YKL-40 and clinical characteristics in PAS group (N=37)

Variable	Correlation Coefficient (r)	P-Value
Number of Previous C/S	+ 0.518	0.001
Maternal Age(years)	+0.084	0.621
Gestational Age(weeks)	-0.462	0.004

When compared to histopathology as the gold standard, ultrasound had a sensitivity of 94.6%, specificity of 95%, PPV of 92.1%, NPV 96.6%, and overall accuracy of 94.85%; as shown in (Table 6). However, it is noteworthy that three cases in the control group were misidentified by ultrasound as having abnormal placentation (False Positives). These discrepancies may be attributed to specific ultrasound markers, such as

prominent placental lacunae or focal loss of the retroplacental clear zone, which can occasionally mimic PAS features in normal pregnancies. Despite these few false-positive findings, the high Negative Predictive Value (96.6%) confirms that ultrasound remains a highly reliable tool for ruling out placenta accreta spectrum (PAS) when compared to histopathology as the gold standard.

Table 6: Diagnostic accuracy of ultrasound for the detection of abnormal placentation.

Ultrasound Findings	Histopathology: PAS Cases (N=37)	Histopathology: Controls (N=60)	Total (N=97)
Abnormal Placentation	35	3	38
Normal Placentation	2	57	59
Total	37	60	97

Discussion

The findings of the present study revealed that patients with abnormal placentation had significantly higher parity and multiple caesarean sections. This result concurs with the research conducted by Kietpierakool et al., who reported that previous caesarean sections were associated with a higher risk of 2.6 of PAS and 1.8 of placenta previa(7) . A retrospective comparison

study showed that patients with anterior placenta previa had significantly higher parity and rates of previous caesarean sections(8) . In their study, Chamua et al., observed a significant increase in placenta previa among those who had three lower segment caesarean sections compared with those who had only two(9) .

In this study, the mean YKL-40 level was considerably higher in the cases than in the controls. This outcome was in accordance with the findings of Bayramoğlu et al., who found a correlation between the diagnosis and severity of PAS and high serum YKL-40 levels. They found that in the PAS group, the mean YKL-40 level was significantly higher than that of both the previa and normal pregnancy groups (10). Similarly, Liu et al reported that the immunohistochemistry showed a significantly higher YKL-40 level in the PAS group than in the control group (11). The study of Karapinar et al., on 60 patients diagnosed with abnormal placentation, concluded that the serum YKL-40 level could be a marker used for detecting placental invasion abnormalities (12).

In the present study, the correlation between maternal serum YKL-40 levels and the severity of PAS was evaluated using Receiver Operating Characteristic curve analysis. The area under the curve was 0.972, indicating a strong significant association between elevated YKL-40 levels and the presence of diagnosed PAS cases. At a cut-off value of 112.68 pg/ml, the marker demonstrated high performance in discriminating between patients with abnormal placentation and the control group, with a sensitivity of 94.6% and a specificity of 100%. These findings suggest that serum YKL-40 levels correlate with the clinical severity of the disease spectrum (accreta, increta, and percreta) rather than serving as a primary diagnostic tool in the third trimester, this differs from the findings of the Bayramoğlu et al. study (10). With a sensitivity of 66% and specificity of 70.37%, the cut-off value for the YKL-40 was determined to be 32.81 ng/ml.

In fact, the extra-villous trophoblast over-invasion, lack of intervening decidua basalis, or a combination of the two, may be the cause of the pathological adhesion of the chorionic villi in the placenta of the PAS patients. The fact that 80% of the PAS patients report a history of CS, myomectomy, and/or curettage operations lends credence to this assumption. According to a study by Gözükarar et al., (13) the YKL-40 intensity was significantly higher in the percreta group than in the increta and accreta groups, and it was positively correlated with depth of invasion and the ratio of depth of invasion to full thickness.

Further, the findings published by Bayramoğlu (10) and other co-authors corroborated this result, which showed that the degree of invasion in PAS is linked to higher concentrations of the YKL-40 and that, among the accreta, increta, and percreta groups, these levels were significantly higher in the increta group than in the accreta group, and in the percreta group than in the increta and accreta groups.

In the present study, several potential confounding factors were analyzed to ensure the validity of YKL-40 as an independent biomarker for Placenta Accreta Spectrum (PAS). While maternal age showed no

significant differences between the groups, other clinical variables such as gestational age at delivery, parity, and the number of previous caesarean sections were significantly higher in the PAS group. These findings are consistent with the established clinical risk profile for placental adhesion abnormalities.

The significant positive correlation with previous Cesarean Sections (CS) in the PAS group suggests that YKL-40 levels increase as the number of surgical scars increases. YKL-40 is a known biomarker for inflammation and tissue remodeling. Each subsequent CS leads to more extensive uterine scarring and chronic inflammation at the site of the previous incision. Since previous CS is the primary risk factor for PAS, the rising YKL-40 levels likely reflect the increased severity of uterine damage, which facilitates the abnormal invasion of trophoblastic tissue. The current data showed a significant negative correlation between YKL-40 and gestational age with higher levels of YKL-40 being associated with earlier (preterm) deliveries because in PAS cases, early delivery is often mandatory due to life-threatening complications such as severe bleeding. Maternal age did not show any significant correlation with YKL-40 levels in either the total population or the PAS group which indicates that the rise in YKL-40 is a specific response to the pathological state of the placenta and uterine scarring, rather than a general consequence of the patient's age. This strengthens the argument for YKL-40 as a specific biomarker for PAS-related complications.

The sensitivity of the ultrasound in diagnosing abnormal placentation, such as placenta accreta spectrum disorders, has been reported to vary widely across studies. Some studies have shown sensitivities with a 33 to 100% range, based on the study population and the criteria employed (14), (15). The present study showed a high ultrasound sensitivity 94.6% and specificity of about 95%.

Limitation:

The present study is subject to some limitations, including a small sample size, a short duration for data collection, and a relatively high investigation cost.

Conclusion

In the third trimester, serum YKL-40 seems to be a promising biomarker linked to the occurrence and clinical severity of placenta accreta spectrum. Although the availability of imaging tools at this point of pregnancy limits its use as a major diagnostic tool, it does exhibit a strong association with the depth of placental invasion. Its strong correlation with the number of previous C-sections highlights the role of scar-mediated pathology, while its negative correlation with gestational age underscores its potential as a predictor for the timing of delivery.

Authors' declaration:

We attest that every figure and table in the manuscript is part of the current investigation. Additionally, the figures and photographs that are not part of the current study have been granted permission to be republished and are attached to the text. On ethical issues, authors sign. Approval-Ethical Clearance: On April 17, 2023, the project was approved under code number (55) by the local ethical committee in (place where the research was conducted or materials were gathered and treated).

Conflict of Interest: None.

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Data availability: Upon reasonable request, the corresponding author will make the data sets generated and/or analyzed during the current work available.

Authors' Contribution:

Study conception & design: (Dr. Najmah M. Meran, Zina E. Mohamed). Literature search: (Dr. Zina E. Mohamed). Data acquisition: (Dr. Zina E. Mohamed). Data analysis & interpretation: (Dr. Najmah M. Meran, Dr. Zina E. Mohamed). Manuscript preparation: (Dr. Zina E. Mohamed). Manuscript editing & review: (Dr. Najmah M. Meran, Zina E. Mohamed).

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دور YKL-40 في تشخيص طيف المشيمة الملتصقة لدى المرضى العراقيين نجمه محمود ميران¹, زينه عماد محمد²

¹ فرع النسائية والتوليد، كلية الطب، جامعة بغداد، بغداد، العراق.
² فرع النسائية والتوليد، مستشفى بغداد التعليمي، مدينة الطب، وزارة الصحة، بغداد، العراق.

الخلاصة

الخلفية: مع ازدياد عدد الولادات القيصرية خلال الخمسين عامًا الماضية، برزت ظاهرة المشيمة الملتصقة كإحدى المشكلات الشائعة المرتبطة بالحمل. تتزايد حالات الإصابة بهذه المشكلة، حيث تشير التقديرات الحديثة إلى أنها تحدث بنسبة تتراوح بين 1/333 و 1/533 من حالات الولادة. وتُظهر الدراسات الحديثة أن بروتين YKL-40 (المعروف أيضًا باسم بروتين الكيتيناز-3 الشبيه 1، وهو بروتين سكري مُفرز يبلغ حجمه حوالي 40 كيلو دالتون) قد يكون له دور في تكوين الأوعية الدموية، وتكاثر الخلايا وتمايزها، بالإضافة إلى إعادة تشكيل المصفوفة خارج الخلية، وغيرها من العمليات الالتهابية.

هدف الدراسة: تقييم العلاقة بين مستويات بروتين YKL-40 في مصل دم الأم وشدة طيف المشيمة الملتصقة.

المنهجية: أجريت دراسة حالة-مقارنة في قسم أمراض النساء والتوليد بمستشفى بغداد التعليمي/بغداد على مدار عام كامل، من 1 حزيران 2023 إلى 1 حزيران 2024. شملت الدراسة 97 امرأة حامل بجنين واحد في الثلث الثالث من الحمل تم تشخيص إصابتهن بطيف التصاق المشيمة (37 مريضة) وأولئك اللواتي لديهن مشيمة في موضعها الطبيعي (60 مريضة)، حضرن إلى المستشفى للولادة الطبيعية أو القيصرية (مجموعة المقارنة). تم فحص مستوى بروتين YKL-40 في مصل الدم لدى المجموعتين.

النتائج: أظهرت هذه الدراسة أن متوسط مستوى بروتين YKL-40 كان أعلى بشكل ملحوظ لدى النساء المصابات بطيف التصاق المشيمة مقارنةً بالنساء ذوات المشيمة الطبيعية. بما أن نقطة القطع لـ YKL-40 هي 112.68 بيكوغرام/مل، فإن مستوى YKL-40 < 112.68 بيكوغرام/مل يرتبط بتكوين المشيمة غير الطبيعي.

الاستنتاج: يبدو أن بروتين YKL-40 في مصل الدم مؤشر حيوي واعد يرتبط بوجود وشدة طيف المشيمة الملتصقة في الثلث الأخير من الحمل. ورغم أن دوره كأداة تشخيصية أساسية محدود بتوفر تقنيات التصوير في هذه المرحلة من الحمل، إلا أنه يُظهر ارتباطًا وثيقًا بعمق غزو المشيمة.

الكلمات المفتاحية: مؤشر حيوي، مشيمة ملتصقة، طيف المشيمة الملتصقة، المشيمة المنزاحة، YKL-40.