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Analysis of changes in serum VEGF, *β*-hCG, and sFlt-1 levels in women with placenta accreta spectrum and the impact on prognosis

https://doi.org/10.1515/jpm-2025-0291
Received May 27, 2025; accepted October 24, 2025;
published online December 3, 2025

Abstract

Objectives: To explore serum vascular endothelial growth factor (VEGF), *β*-subunit human chorionic gonadotropin (*β*-hCG), and soluble Fms-like tyrosine kinasereceptor 1 (sFlt-1) levels in pregnant women with placenta accreta spectrum (PAS) and their prognostic implications.

Methods: Serum levels were measured in PAS patients and non-PAS controls. Depending on the depth of placental penetration into the uterine wall, PAS patients were further classified into placenta accreta, placenta increta and placenta percreta subgroups. Diagnostic efficacy of individual biomarkers and combined indices was evaluated using receiver operating characteristic curves. Correlations between biomarker levels, disease severity, and prognosis were analyzed.

Results: Serum levels of VEGF and *β*-hCG showed significant positive correlations with the extent of PAS invasion, whereas sFlt-1 levels were inversely associated with disease progression. Combined pregnancy complications, elevated serum VEGF levels and decreased serum sFlt-1 levels were risk factors for poor prognosis in patients with PAS. The AUC values of the indicators combined to predict the diagnosis and prognosis of patients with PAS were greater than serum VEGF, hCG, and sFlt-1 levels alone.

Conclusions: Serum levels of VEGF, *β*-hCG, and sFlt-1 demonstrate the potential to differentiate between women with and without PAS, and further exhibit a correlation with the depth of myometrial invasion in PAS cases. The combined use of these serum markers enhances both the sensitivity and specificity of prenatal diagnosis and prognostic assessment for PAS compared to individual markers, thereby offering valuable guidance for clinical diagnosis and management of PAS.

Keywords: placenta accreta spectrum; VEGF; β-hCG; sFlt-1; prognosis

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Introduction

Placenta accreta spectrum (PAS) is a severe obstetric complication characterized by abnormal invasion of cytotrophoblast cells at the endometrial-myometrial junction. This condition is classified into three categories: placenta accreta, increta, and percreta, based on the extent of placental infiltration into the myometrial layer of the uterus [1]. Under normal circumstances, the placenta can detach from the uterine wall after delivery, but in the presence of PAS, some or all of the placenta remains attached to the uterine wall after delivery, which can lead to severe postpartum hemorrhage and shock [2]. PAS is a contributor to poor maternal and infant outcomes, and it is critical to find reliable indicators early on to diagnose PAS and assess patient prognosis. Clinical data show that abnormal placental vascular growth and development and associated vascular growth factor abnormalities are the main pathogenesis of PAS [3]. Vascular endothelial growth factor (VEGF) can directly stimulate the proliferation and differentiation of vascular endothelial cells and promote neoangiogenesis [4]. Soluble Fms-like tyrosine kinasereceptor 1 (sFlt-1) is a soluble isoform of VEGF receptor-1 (VEGFR-1) generated through alternative mRNA splicing. This secreted glycoprotein retains the extracellular ligand-binding domain of VEGFR-1 while lacking transmembrane and intracellular kinase domains. Functionally, sFlt-1 binds and antagonizes VEGF to inhibit its angiogenic function [5, 6]. Measurement of serum VEGF and sFlt-1 levels is gaining recognition as a diagnostic adjunct for suspected PAS disorders, with emerging prognostic value in predicting disease progression severity [7, 8]. Human chorionic gonadotropin (hCG), a glycoprotein hormone composed of α and β subunits, is primarily secreted by trophoblasts. This hormone holds critical implications for confirming normal gestation, diagnosing gestational-specific disorders, and screening fetal congenital anomalies or developmental pathologies [9, 10]. *β*-subunit hCG (*β*-hCG) is synthesized by trophoblastic cells and predominantly secreted into maternal circulation, while placental tissue concentrations remain comparatively low. During the second trimester, this biomarker exhibits high detectability and stability, serving as a reliable indicator of trophoblastic activity. Studies demonstrate elevated *β*-hCG levels in PAS patients compared to non-PAS controls, with concentrations progressively increasing across PAS severity [11]. However, there is no clear report about the relationship between each index and the prognosis of patients with PAS.

Therefore, the aim of this study was to investigate the changes in serum VEGF, *β*-hCG, and sFlt-1 levels in women with PAS and their effects on prognosis, so as to provide a reference for the early assessment of the prognosis of patients with this disease.

Materials and methods

Research object

A retrospective analysis was conducted on the clinical data of 120 pregnant women giving birth at the Jiangsu Taizhou People's Hospital from January 2017 to December 2020. The study group comprised 68 pregnant women diagnosed with PAS, while the control group consisted of 52 women with uncomplicated physiological pregnancies (non-PAS).

Inclusion criteria: ① underwent routine antenatal ultrasonography prior to delivery; ② antenatal PAS high-risk factors such as history of uterine incision, cesarean section, multiple deliveries, induced abortion, advanced maternal age; ③ gestational weeks ≥ 32 weeks; ④ single pregnancy; ⑤ complete antenatal examination data.

Exclusion criteria: ① hepatic and renal insufficiency; ② incomplete clinical data; gynecological malignant tumors; ③ fetal anomalies; ④ fetal chromosomal abnormalities; ⑤ multiple pregnancies.

Diagnostic criteria and classification of PAS

The prenatal diagnosis of PAS was primarily based on ultrasonography [12–14]. The following sonographic features, in accordance with the International Federation of Gynecology and Obstetrics (FIGO) recommendations [15], were utilized for the evaluation of PAS: the presence of placental lacunae, absence of the retroplacental clear zone (also known as the hypoechoic space), abnormalities at the utero-bladder interface, and color Doppler findings such as hypervascularity and bridging vessels. The diagnosis was further confirmed either by intraoperative identification of a "glued" appearance indicating placental adherence to the uterine wall in hysterectomy specimens, or by postoperative histopathological examination of focally excised tissue.

The grading of PAS into accreta, increta, and percreta was validated by postoperative pathological examination. According to the FIGO classification [15], placenta accreta was characterized by placental villi attached to the myometrium; placenta increta was defined by villi invading into the myometrial layer; and placenta percreta was confirmed by villi penetrating through or breaching the uterine serosa.

Study design and methods

Maternal clinical data were collected and analyzed, including age, gestational age, area of PAS, parity, history of cesarean section, placental morphology, and the presence of adverse pregnancy outcomes.

Enzyme-linked immunosorbent assay was conducted to detect serum VEGF and sFlt-1 levels in patients (kits provided by Shanghai Bogu Biological Technology Co., Ltd., Shanghai, China). Serum *β*-hCG level was detected by magnetic particle chemiluminescence method, and the kit was provided by Xiamen Innodx BIOTECH Co., Ltd. (Fujian, China).

Serum levels of VEGF, *β*-hCG, and sFlt-1 were measured and compared between the PAS group and the non-PAS group, as well as among the placenta accreta ($n = 25$), placenta increta ($n = 38$), and placenta percreta ($n = 5$) subgroups. The diagnostic value of each index for PAS was evaluated. Correlation analyses were performed to assess the relationship between each index and the depth of invasion in PAS (accreta, increta, and percreta). All patients underwent surgical treatment, and based on the occurrence of postoperative adverse pregnancy outcomes, the study cohort was categorized into a group with better prognosis ($n = 51$) and a group with poor prognosis ($n = 17$). The impact of serum VEGF, *β*-hCG, and sFlt-1 levels on patient prognosis was subsequently analyzed.

Statistical analysis

SPSS 22.0 software was taken to process the data. Enumeration data were expressed as % and compared by χ^2 test. Measurement data were expressed as (±s) after the normal test, and comparatively assessed using *t*-test between two groups or one-way ANOVA between multiple groups. The diagnostic value of PAS was analyzed by the receiver operating characteristic (ROC) curve using the levels of serum VEGF, β-hCG, and sFlt-1. The correlation between serum VEGF, β-hCG and sFlt-1 levels and the severity of PAS was examined by spearman test, and the influencing factors of the prognosis of patients with PAS were analyzed by multivariate logistic regression. Differences were statistically significant at $p < 0.05$.

Results

Serum VEGF, β-hCG and sFlt-1 levels in the PAS group and non-PAS group

The serum VEGF and β-hCG levels in the PAS group ($n = 68$) were higher than those in the non-PAS group ($n = 52$), and the sFlt-1 levels were lower ($p < 0.05$, Figure 1).

Diagnostic value of serum VEGF, β-hCG, and sFlt-1 levels for PAS

The AUC value of the combined test of each index for the diagnosis of PAS was greater than that of serum VEGF, β-hCG, and sFlt-1 levels alone ($p < 0.05$), as shown in Table 1 and Figure 2.

Table 1: Diagnostic value of serum VEGF, β-hCG, and sFlt-1 levels for PAS.

Indicators	Cut-off value	AUC	SE	95%CI
VEGF	312.73 μg/L	0.737[a]	0.046	0.647~0.827
β-hCG	276.51 ng/mL	0.818[a]	0.04	0.740~0.897
sFlt-1	1.89 μg/L	0.716[a]	0.047	0.624~0.808
Combined		0.881	0.031	0.821~0.941

Compared with the combined, [a]$P < 0.05$.

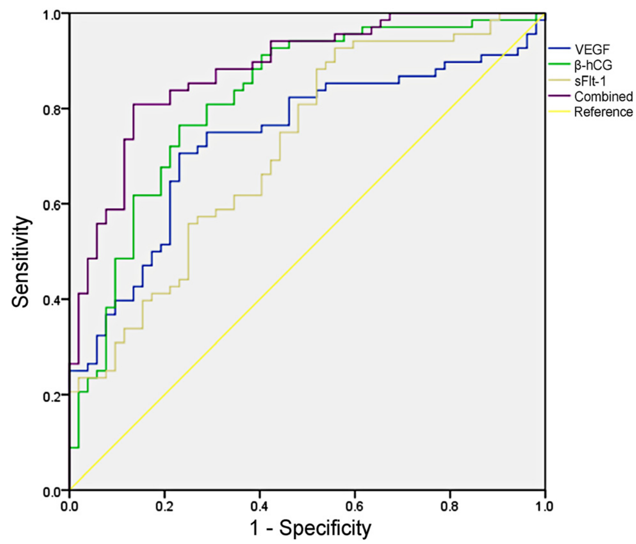

Figure 2: ROC curves of serum VEGF, β-hCG, and sFlt-1 levels for the diagnosis of PAS.

Serum VEGF, β-hCG, and sFlt-1 levels in patients with different severity of PAS

Based on the depth of villous invasion into the myometrium, 68 cases with PAS were classified into three subgroups: placenta accreta ($n = 25$), placenta increta ($n = 38$), and placenta percreta ($n = 5$). Comparing serum VEGF and β-hCG levels, the placenta percreta group was the highest, followed by the placenta increta group, and then the placenta accreta group. sFlt-1 levels were highest in the placenta accreta group, followed by the placenta increta group, and then the placenta percreta group ($p < 0.05$, Figure 3).

Correlation analysis of serum VEGF, β-hCG, and sFlt-1 levels with the severity of PAS

Serum VEGF and β-hCG levels were positively correlated with the severity of PAS, and sFlt-1 levels were negatively correlated with the severity of PAS ($p < 0.05$, Table 2).

Univariate analysis of prognosis of patients with PAS

The area of PAS in the poor prognosis group was larger than that in the better prognosis group. The proportion of

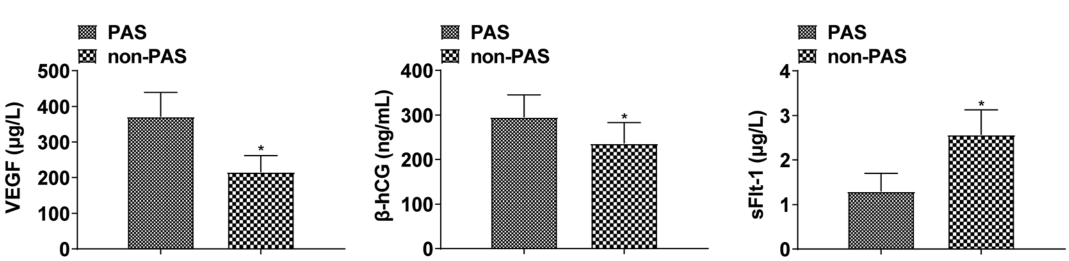

Figure 1: Comparison of serum VEGF, β-hCG, and sFlt-1 levels in the PAS group and the non-PAS group(*$p < 0.05$ compared with the PAS group).

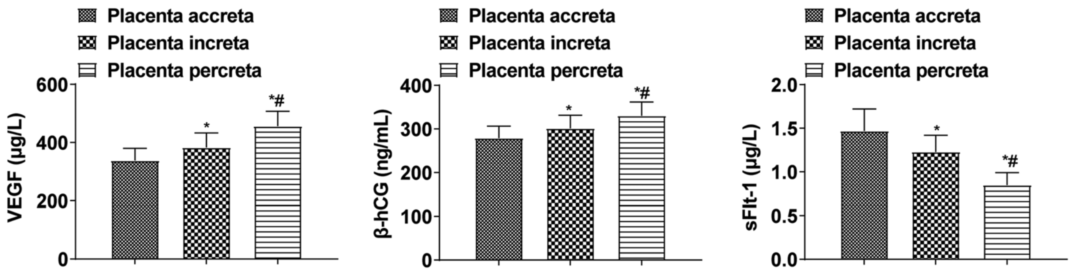

Figure 3: Comparison of serum VEGF, β-hCG and sFlt-1 levels in patients with different severity of PAS (*p < 0.05 compared with the placenta accreta group; #p < 0.05 compared with the placenta increta group).

Table 2: Correlation analysis of serum VEGF, β-hCG and sFlt-1 levels with the severity of PAS.

Indicators	*r*	p-Value
VEGF	0.407	< 0.001
β-hCG	0.546	< 0.001
sFlt-1	−0.371	< 0.001

pregnant women with abnormal placental morphology and combined pregnancy complications was higher, VEGF and β-hCG were higher, and sFlt-1 was lower than those in the better prognosis group ($p<0.05$, Table 3).

Multifactorial analysis of the prognosis of patients with PAS

Combined pregnancy complications, elevated serum VEGF levels and decreased serum sFlt-1 levels were risk factors for poor prognosis in patients with PAS ($p < 0.05$, Table 4).

Table 3: Univariate analysis of prognosis of patients with PAS.

Factors	Good prognosis group (*n* = 51)	Poor prognosis group (*n* = 17)	χ^2/t	p-Value
Age	28.96 ± 4.05	30.28 ± 3.63	1.193	0.237
Gestational age	35.01 ± 2.74	35.09 ± 2.88	0.103	0.918
Area of PAS	22.63 ± 3.16	26.18 ± 4.21	3.681	< 0.001
Multipara	30	8	0.716	0.398
Previous history of cesarean section	31	9	0.324	0.569
Abnormal placental morphology	20	12	5.037	0.025
Adverse pregnancy history	12	8	3.4	0.065
Combined pregnancy complications	19	13	7.87	0.005
VEGF (μg/L)	346.89 ± 50.61	445.41 ± 43.09	7.195	< 0.001
β-hCG (ng/mL)	279.03 ± 47.62	344.43 ± 31.38	5.279	< 0.001
sFlt-1 (μg/L)	1.38 ± 0.26	1.02 ± 0.21	5.167	< 0.001

Predictive value of serum VEGF, β-hCG, and sFlt-1 levels on the prognosis of patients with PAS

The AUC value of the combined test of each index for predicting the prognosis of patients with PAS was greater than that of serum VEGF, β-hCG, and sFlt-1 levels tested individually ($p < 0.05$, Table 5 and Figure 4).

Discussion

The etiology of PAS is still unclear, and it is currently believed that it is mainly caused by uterine dysplasia or injury, interruption and partial loss of the decidua, and invasion of trophoblasts in the chorionic villi of placenta into the myometrium, or even breakthrough of the plasma membrane layer. PAS is one of the serious complications in obstetrics, which can lead to maternal hemorrhage, shock, uterine perforation, secondary infection, and even death [16, 17]. The development of the placenta throughout pregnancy is associated with multiple modulations of placental vascular growth and differentiation, and these changes occur simultaneously on both the maternal and placental surfaces, including recasting of the uterine spiral arteries as well as vascularization of the placenta [18, 19].

It was found in this work that the serum VEGF and β-hCG levels of the PAS group were higher than those of the non-PAS group, and the sFlt-1 level was lower. In addition, ROC curve analysis demonstrated that the AUC values for diagnosing PAS using VEGF, β-hCG, and sFlt-1 individually were 0.737, 0.818, and 0.716, respectively, while the combination of all three markers achieved an AUC of 0.881. These results indicate that each marker alone has substantial diagnostic value, and that the combined panel performs better than any single biomarker. Furthermore, the optimal cut-off values for VEGF, β-hCG, and sFlt-1 were determined to be 312.73 μg/L, 276.51 ng/mL, and 1.89 μg/L, respectively. Each of

Table 4: Multifactorial analysis of prognosis of patients with PAS.

Factors	β	SE	wald χ2	OR	95%CI	p-Value
Abnormal placental morphology	0.583	0.306	3.63	1.791	0.983~3.263	0.057
Combined pregnancy complications	0.923	0.218	17.926	2.517	1.642~3.859	< 0.001
VEGF	0.764	0.25	9.339	2.147	1.315~3.504	0.002
β-hCG	0.396	0.207	3.66	1.486	0.990~2.229	0.056
sFlt-1	−0.913	0.345	7.003	0.401	0.204~0.789	0.008

Table 5: Predictive value of serum VEGF, β-hCG, and sFlt-1 levels on the prognosis of patients with PAS.

Indicators	Cut-off value	AUC	SE	95%CI
VEGF	397.28 μg/L	0.724[a]	0.072	0.582~0.866
β-hCG	308.94 ng/mL	0.755[a]	0.072	0.614~0.897
sFlt-1	1.15 μg/L	0.684[a]	0.07	0.547~0.821
Combined		0.872	0.052	0.770~0.974

Compared with the combined, [a]P < 0.05.

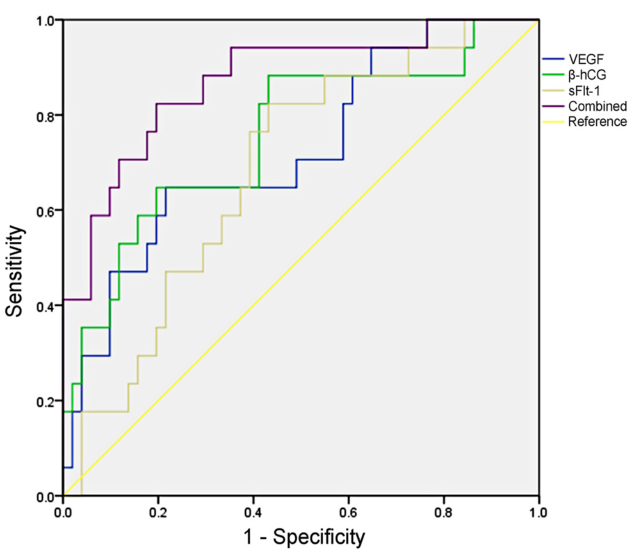

Figure 4: ROC curves of serum VEGF, β-hCG, and sFlt-1 levels to predict prognosis in patients with PAS.

these values represents the threshold at which the optimal balance between sensitivity and specificity was achieved for distinguishing PAS from non-PAS cases.

Abnormal angiogenesis can lead to dysplasia of the decidua and excessive invasion of the trophoblastic layer, resulting in PAS. Various vascular growth factors are involved in placental angiogenesis, among which VEGF is the mitogen with the highest specificity for endothelial cells and the strongest pro-angiogenic effect, which can directly stimulate vascular endothelial cells to move, proliferate, and divide, increase microvessel permeability, and promote neovascularization [20]. sFlt-1 has been identified as an antagonist of VEGF, and may exert regulatory influence on trophoblast hyperinvasion and pathological vascular remodeling in PAS. hCG plays a well-characterized role in implantation and placental development. Current evidence recognizes five distinct hCG isoforms: regular hCG (r-hCG), hyperglycosylated hCG (H-hCG), pituitary hCG (p-hCG), free β-hCG, and hyperglycosylated free β-hCG (H-β-hCG), each demonstrating unique biological activities [21]. Notably, the free β-subunit and its hyperglycosylated variant exhibit specific associations with malignant pathologies [9]. Emerging clinical data demonstrate elevated β-hCG concentrations in PAS cases compared to uncomplicated pregnancies [22, 23]. Pathophysiologically, impaired placental villous vascular exchange in PAS may induce hypoxia, triggering compensatory β-hCG hypersecretion [24–26].

In placenta accreta, there is no obvious abnormality in the attachment position of the placenta in the uterine wall, and there is usually no obvious bleeding during pregnancy, nor does it significantly affect the physiological function of the placenta, and the development of the fetus is largely unaffected. Once placenta percreta occurs, it may lead to uterine rupture, causing severe abdominal pain and serious bleeding, endangering the lives of mother and baby [27, 28]. The present study demonstrated that as the degree of PAS increased, the serum VEGF level also elevated. Meanwhile, the serum sFlt-1 level exhibited a negative correlation with the degree of PAS. Homeostatic regulation of placental angiogenesis requires precise dynamic equilibrium between VEGF-mediated vascular proliferation (pro-angiogenic) and sFlt-1-induced signaling suppression (anti-angiogenic). This molecular interplay governs physiological placentation and controlled trophoblast invasion through coordinated modulation of endothelial permeability and vascular remodeling processes [29]. Elevated VEGF promotes placental neovascularization and trophoblast invasiveness, potentiating PAS pathogenesis. Conversely, sFlt-1 binds irreversibly to VEGF, neutralizing its biological activity while independently inducing endothelial dysfunction through vascular hyperpermeability and structural destabilization [30, 31].

Previous studies substantiate our observations, documenting reduced sFlt-1 expression in PAS compared to normal controls [32, 33]. Complementary evidence confirms VEGF-A's critical role in modulating trophoblast invasion [34], with signaling blockade effectively inhibiting cytotrophoblast penetration [29].

PAS is prone to cause maternal hemorrhage, uterine perforation, secondary infections, death, and may also cause hemorrhagic shock, infections, and other complications, so it is crucial to analyze the risk factors affecting the prognosis of women with PAS [35]. The univariate analysis and multifactorial analysis conducted in our study identify concurrent pregnancy complications, elevated serum VEGF, and reduced sFlt-1 as prognostic markers for adverse outcomes in PAS. Mechanistically, VEGF-driven angiogenesis facilitates placental neovascularization through endothelial cell proliferation, while sFlt-1 competitively inhibits VEGF bioactivity, inducing endothelial dysfunction and vascular malformation. In cases of endometrial injury or congenital uterine anomalies, impaired spiral artery remodeling creates a hypoxic placental microenvironment. This hypoxia suppresses sFlt-1 expression while upregulating VEGF. The resultant angiogenic imbalance drives pathological trophoblast invasion into the myometrium to compensate for perfusion deficits, ultimately exacerbating clinical outcomes [36]. Further ROC analysis revealed that serum levels of VEGF, β-hCG, and sFlt-1 exhibited AUC values of 0.724, 0.755, and 0.684, respectively, for predicting the prognosis of patients with PAS. The combination of all three biomarkers achieved a superior AUC of 0.872, demonstrating enhanced predictive performance. The optimal cut-off values for VEGF, β-hCG, and sFlt-1 were identified as 397.28 μg/L, 308.94 ng/mL, and 1.15 μg/L, respectively, with each value representing the threshold that best balances sensitivity and specificity for predicting PAS prognosis. This robust analysis reinforces the credibility of serum VEGF, β-hCG, and sFlt-1 as significant prognostic predictors in PAS.

Our study acknowledges several limitations that warrant consideration. First, the cross-sectional design and relatively limited sample size may compromise the generalizability of our findings. Future studies should prioritize longitudinal designs with larger cohort sizes to rigorously validate the diagnostic and prognostic utility of biomarkers in PAS. Single time-point measurements, while informative, are insufficient for analyzing the temporal trajectory of pathophysiological progression. Second, although our univariate analysis did not reveal significant prognostic associations between some maternal characteristics and outcomes, multivariate analyses incorporating additional variables such as body mass index (BMI), hypertension status, and parity are necessary to account for potential confounding factors. Lastly, the nonsignificant correlation of β-hCG with prognosis may be attributable to both the limited sample size and inherent measurement variability, including cross-reactivity risks, analytical discrepancies across commercial platforms, and biological fluctuations dependent on gestational age, despite adherence to standardized calibration protocols.

Conclusions

In conclusion, changes in serum VEGF, β-hCG, and sFlt-1 levels in women with PAS are related to the severity of the disease, and the combination of these indicators has predictive value for the prognosis of patients with PAS.

Research ethics: All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or National Research Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All subjects was approved by Jiangsu Taizhou People's Hospital (No. 20160718TZPH).
Informed consent: Informed consent was obtained from all individuals included in this study, or their legal guardians or wards.
Author contributions: P. S designed the research study. D.M. P. and Y.L. Z. performed the research. D.M. P. and Y.L. Z. provided help and advice on the experiments. P.S. analyzed the data. P.S. wrote the manuscript. Y.L. Z. reviewed and edited the manuscript. All authors have accepted responsibility for the entire content of this manuscript and approved its submission.
Use of Large Language Models, AI and Machine Learning Tools: None declared.
Conflict of interest: The authors state no conflict of interest.
Research funding: None declared.
Data availability: The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

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