Original Article

DOI: 10.4274/anajog.galenos.2026.32932

Anat J Obstet Gynecol Res 2026;3(1):21-28

Hypoxia-Inducible Factor 1-Alpha (HIF-1α) Decidual Expression Levels in Placenta Accreta Spectrum and its Effect on Abnormal Trophoblastic Invasion

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ABSTRACT

Purpose: Placenta accreta spectrum (PAS) is a condition characterized by abnormal trophoblastic invasion of the decidua and is associated with significant maternal and fetal morbidity and mortality. Hypoxia-inducible factor 1-alpha (HIF-1α) is a transcription factor that increases neovascularization in hypoxic environments. The aim of this study was to investigate the role of HIF-1α in abnormal trophoblastic invasion observed in PAS.

Methods: This prospective study included 29 PAS-diagnosed patients (Group 1) and 29 healthy controls with a history of prior [cesarean section (CS); Group 2]. Decidual tissue samples from participants were collected and stained with anti-HIF-1α antibody using immunohistochemical methods. Staining was evaluated both qualitatively and quantitatively. In qualitative assessment, the number of stained nuclei was determined by a pathologist. Quantitative assessment was performed using ImageJ and GraphPad Prism software, with staining intensity calculated in pixels.

Results: Staining intensity graded as 2 or 3 was significantly higher in Group 1 compared to Group 2 in qualitative analysis ($p=0.006$, $p<0.001$, respectively). The percentage of positive staining area (%), the average positive region area (in pixels) and normalized average positive region area (%) were significantly greater in Group 1 compared to Group 2 on quantitative analysis ($p<0.001$, $p=0.019$, $p=0.044$, respectively).

Conclusion: HIF-1α expression in decidual tissue is greater in PAS-diagnosed patients compared to healthy pregnant women with prior CS. This suggests that abnormal trophoblastic invasion in PAS may be due to hypoxia in the decidual tissue, which could lead to neovascularization driven by increased HIF-1α expression.

Keywords: Placenta accreta, hypoxia-inducible factor 1-alpha, placenta diseases

INTRODUCTION

During placental development, trophoblasts physiologically invade the endometrium, typically reaching the Nitabuch's layer, which is a fibrous connective tissue degeneration between the decidua and myometrium.[1] When this invasion exceeds the Nitabuch's layer and extends into deeper tissues, it is referred to as placenta accreta spectrum (PAS). The International Federation of Gynecology and Obstetrics (FIGO)[2] advocates that PAS encompasses a range of abnormal placental invasions, from partial penetration into the

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Received: 01.04.2026 **Accepted:** 28.04.2026 **Publication Date:** 13.05.2026

Cite this article as: Aslancan Bayram R, Acar S, Dursun ŞK, et al. Hypoxia-inducible factor 1-alpha (HIF-1α) decidual expression levels in placenta accreta spectrum and its effect on abnormal trophoblastic invasion. Anat J Obstet Gynecol Res. 2026;3(1):21-28

myometrium to more severe forms such as invasion through the uterine serosa and into adjacent organs such as the bladder and parametrium.

The prevalence of PAS has increased dramatically over the years, in parallel with rising cesarean section (CS) delivery rates and advanced maternal age. In a systematic review conducted in 2019, among 5.8 million births, 7,001 cases were diagnosed with PAS, corresponding to a prevalence of 0.17%.[3] Management of PAS requires experience and a multidisciplinary approach; thus, affected patients should be followed in tertiary care centers from the time of diagnosis through the postpartum period. Treatment often involves segmental placental resection or hysterectomy and carries substantial risks of maternal and fetal morbidity and mortality, including preterm birth, bladder injury, and massive hemorrhage.[4]

The pathogenesis of PAS is thought to involve defective Nitabuch's layer formation and impaired regulation of trophoblastic invasion. However, its exact mechanism remains incompletely understood although it is known that decidual natural killer cells, pregnancy related hormones, proteolytic enzymes, integrins and growth factors, such as placental growth factor and vascular endothelial growth factor (VEGF), are involved in the regulation of trophoblastic invasion.[5,6] Risk factors such as previous CS delivery, placenta previa, obesity, advanced maternal age, and a history of postpartum hemorrhage are known to increase the likelihood of PAS.

In recent years, molecular studies have contributed significantly to our understanding of PAS. A study examined the expression of sirtuin-2 and sirtuin-7 proteins in placental tissues of patients diagnosed with PAS and healthy controls. The authors found sirtuin-7, which is a regulatory protein of epithelial-mesenchymal transition, was reduced in PAS compared to controls.[7] Another study revealed that serum levels of soluble fms-like tyrosine kinase-1, an inhibitor of VEGF, were significantly lower in PAS patients.[8] These findings suggest that elevated VEGF activity may play a key role in the pathogenesis of PAS.

Hypoxia-inducible factor 1-alpha (HIF-1α) is an oxygen-sensitive transcription factor that is activated under hypoxic conditions. It promotes neovascularization by increasing the expression of proangiogenic factors, particularly VEGF.[9] HIF-1α is also known to play a role in abnormal vascularization seen in tumor invasion and metastasis.[10] In PAS, the hypoxic environment resulting from previous uterine interventions may lead to increased HIF-1α expression because of poor oxygenation in the damaged endometrial and myometrial tissues, triggering VEGF production and contributing to abnormal trophoblastic invasion.

The aim of this study was to investigate HIF-1α expression in decidual tissue samples taken from the invasion site of the placenta in patients diagnosed with PAS and in healthy pregnant women, in order to explore the potential role of HIF-1α in the pathogenesis of abnormal placental invasion in PAS.

METHODS

Study Design and Setting

The study was designed as a prospective study and conducted between September 1, 2024, and January 1, 2025, at the Departments of Obstetrics and Gynecology and Pathology of Başakşehir Çam and Sakura City Hospital. The research was granted ethical approval by the Ethics Committee of Başaksehir Çam and Sakura City Hospital (protocol number: KAEK-11/14.08.2024.103, date: 19.08.2024) and was conducted in compliance with Declaration of Helsinki. Patients who delivered at our hospital and had suspected PAS based on prenatal ultrasound were included in the study group (Group 1). The diagnosis of PAS was established intraoperatively by confirming placental invasion and subsequently confirmed by histopathological examination. Healthy pregnant women with a history of previous CS delivery who gave birth at our hospital comprised the control group (Group 2). Data included patients' demographic variables, neonatal birth weight, and gestational age at delivery. In addition, the type of surgical procedure and FIGO staging were recorded for patients in Group 1.

Patients aged between 18 and 40 years, diagnosed with PAS and undergoing delivery at our hospital at a gestational age beyond 32 weeks were included in Group 1. This gestational age threshold was selected in accordance with standard clinical practice, as planned surgical management for PAS is typically performed after 32 weeks of gestation. Similarly, pregnant women aged 18-40 years, who underwent previous sections, were beyond 32 weeks of gestation and had no PAS diagnosis, were included in Group 2. Patients diagnosed with preeclampsia, hypertension or gestational diabetes were excluded from both groups. Those who did not provide written informed consent were not included in the study. Of note, in Group 1, placental and myometrial tissue samples from two patients who underwent segmental resection were sent to pathology but they were excluded from the study as decidual tissue was not identified in these specimens. The patient selection flowchart for Group 1 is shown in Figure 1. Group 2 was composed of patients who met the inclusion criteria and had planned CS in the same hospital due to a history of previous CS. The study included all consecutive PAS cases meeting the inclusion criteria between September 1, 2024, and January 1, 2025. Given the rarity of PAS, no formal sample size calculation was performed. A control group of equal size was selected for comparison.

Collection of Pathology Specimens

Following hospitalization for planned delivery, patients with a diagnosis of PAS underwent surgery and total and supracervical hysterectomy and segmental resection specimens (uterus and placenta) were sent to the pathology department in 10% formalin solution. From these specimens, the pathologist obtained a 1 × 1 cm section of decidual tissue from the central

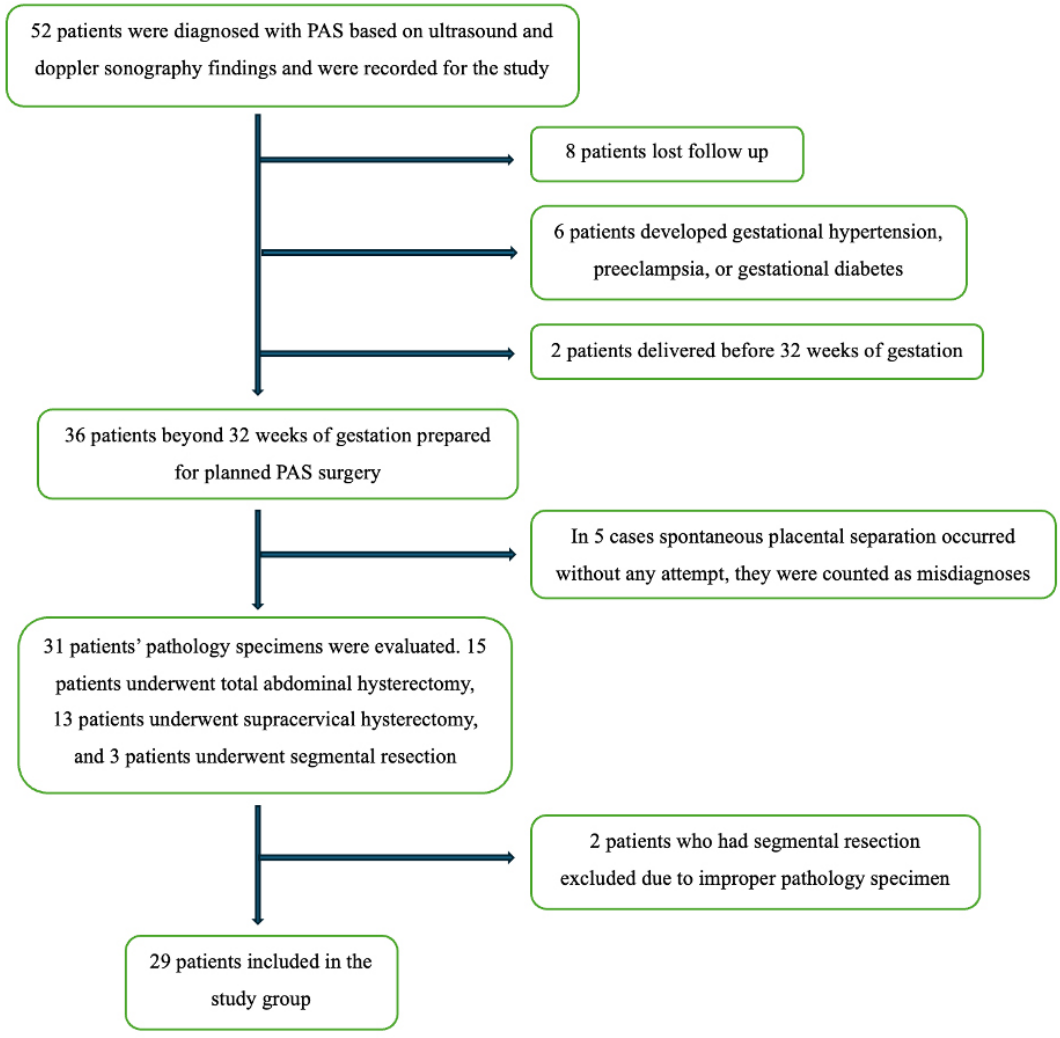

Figure 1. Patient selection flowchart for Group 1

PAS: Placenta accreta spectrum

area of the uterine wall with placental invasion. In Group 2, decidual tissue samples measuring 1 × 1 cm in width and 5 mm in depth were similarly obtained from the central area of the placental implantation site during CS. A low-lying placenta was not observed in any of the patients in Group 2.

Preparation of Pathology Specimens for Immunohistochemical Staining

Upon receipt of each specimen at the Pathology Department, routine tissue sectioning was performed. Decidual tissue samples with confirmed placental invasion in Group 1 and decidual tissue from the central site of placental attachment in Group 2 were prepared. The specimens were fixed in formalin at room temperature, processed through routine tissue processing, and embedded in paraffin. Sections of 3 μm thickness were cut using a microtome.

Immunohistochemical Staining Protocol

Immunohistochemical (IHC) staining for HIF-1α was performed using the BenchMark XT autostainer (Ventana Medical Systems, Roche Diagnostics). The sections were deparaffinized and subjected to antigen retrieval using the CC1 (cell conditioning) solution for 60 min at 60 °C. The primary antibody, HIF-1α (PA1-16601, Thermo Fisher Scientific), was diluted 1:100 in Dulbecco's phosphate-buffered saline containing 1% bovine serum albumin according to the manufacturer's instructions. Approximately 10 μL of the diluted antibody was applied to each section. The primary antibody incubation was carried out for 60 min at 37 °C. Following primary antibody incubation, the slides were counterstained with Hematoxylin II for 12 min to provide nuclear contrast. Then the chromogen solution was applied to visualize the immunoreaction. As part of the protocol validation, positive control slides with known HIF-1α expression and negative control slides incubated with an isotype control antibody were included to confirm the specificity of staining.

Evaluation of Staining Results

HIF-1α stained sections were mounted with a permanent mounting medium and imaged using a brightfield microscope

(Nikon, ECLIPSE Ci-L 718169). Images were captured under 4x, 10x and 20x magnification to ensure consistent visualization across all samples. The area ratio (%) of HIF-1α staining was quantified using ImageJ software (National Institutes of Health, Bethesda, MD, USA). Five random high-power fields for each sample were selected, and the stained area was segmented using color deconvolution. Thresholding was applied to isolate the chromogen signal from the background, and the percentage of the positively stained area relative to the total tissue area was calculated.

Quantification of HIF-1α Positive Area, Average Positive Region Area and Total Number of Positive Regions

The positive area of fluorescence was quantified after acquiring IHC staining images using ImageJ. A region of interest covering the entire image (pixels) was selected for analysis. The original image was converted to grayscale to simplify the analysis by reducing it to intensity values. Otsu's thresholding method was applied to distinguish positive staining regions from the background.[11] Pixels with intensity values above the calculated threshold were classified as positive. The binary mask (resulting from thresholding) was analyzed, and the number of positive pixels was counted. This count represents the total positive staining area in pixels.

The total image area was calculated as the product of the image's width and height in pixels (Eq. 1) using the following formula:

Total image area (pixels) =
Image width x image height (1)

The positive staining area in pixels was divided by the total image area in pixels, and the result was multiplied by 100 to obtain the percentage (Eq. 2):

Positive staining area (%) =
[Positive area (pixels)/total image area (pixels)] x 100 (2)

Furthermore, the total number of labeled regions (**Eq. 3**) was counted in order to understand the distribution and fragmentation of HIF-1α expression across the tissue.

Average positive region area (pixels) =
Σ Region areas (pixels)/total number of positive regions (3)

As a last step, the average positive region area was normalized to the total image area (Eq. 4) for inter-sample comparisons.

Normalized avg positive region area (%)
= [(Avg positive region area (pixels)/
total image area (pixels)] x 100 (4)

Chromogen Intensity Analysis

After isolating positively stained regions, the chromogen intensity of the HIF-1α positive areas was analyzed. The binary mask created during positive area quantification was applied to the original image to isolate positively stained regions. The isolated regions were converted to grayscales to enable intensity measurements. The mean chromogen intensity of the positive regions was calculated by extracting non-zero-pixel values (pixels with staining) and averaging their grayscale intensity values (Eq. 5). A histogram of staining intensity distribution of HIF-1α (Figure 2A) and H&E (Figure 2B) was plotted to visualize the range and frequency of chromogen intensity values, providing an overview of staining variability.

Mean intensity (grayscale) =
Σ Region intensities/total number of positive regions (5)

The mean intensity of positively stained regions was also standardized relative to the maximum grayscale value of 255. In order to calculate mean intensity, this was normalized as a percentage of the maximum grayscale intensity (Eq. 6):

Normalized mean intensity (%) =
Mean intensity (grayscale)/255) x 100 (6)

The intensity and percentage of HIF-1α staining were also blindly evaluated by a pathologist. Slide images at different magnifications were recorded for each patient. The qualitative staining intensities determined by the pathologist were calculated based on the number of stained nuclei and staining intensity was classified on a four-point ordinal scale (0: no staining, 1: weak, 2: moderate, 3: strong). To compare the distribution of staining intensities between the two groups, a Pearson's chi-square test was performed. In addition, to evaluate whether there was a significant trend across the ordered staining categories, a linear-by-linear association test (Mantel-Haenszel test for trend) was also applied.

Statistical Analysis

The data were analyzed using SPSS for MacOS, version 20.0 (IBM Inc., Armonk, NY, USA). The normality of distribution for continuous variables was assessed using the Shapiro-Wilk test. Continuous variables are expressed as mean ± standard deviation (SD) for normally distributed data, or as median with interquartile range (Q1-Q3) for non-normally distributed data. Categorical variables are presented as frequency (percentage). The significance of differences in means between groups was assessed using Student's t-test for normally distributed data and the Mann-Whitney U test for non-normally distributed data. Statistical differences between categorical variables were evaluated using the chi-square test. Quantitative data obtained from ImageJ analysis were compiled and analyzed using GraphPad Prism (version 8.0.2, GraphPad Software). The mean percentages of HIF-1α staining area between groups were compared using the Independent Samples t-test. Data were reported as mean ± SD, and results with p values <0.05 were considered statistically significant.

RESULTS

The full study cohort numbered 58 patients, subdivided into the PAS (Group 1; n=29) and control (Group 2; n=29) groups. Demographic characteristics and comparison between the groups is shown in Table 1. The groups did not differ in terms of age, body mass index, and presence of comorbidities. However, gravida, parity, and number of previous CS deliveries were significantly higher in Group 1 compared to Group 2. Gestational age at delivery and birth weight were significantly higher in Group 2 compared to Group 1.

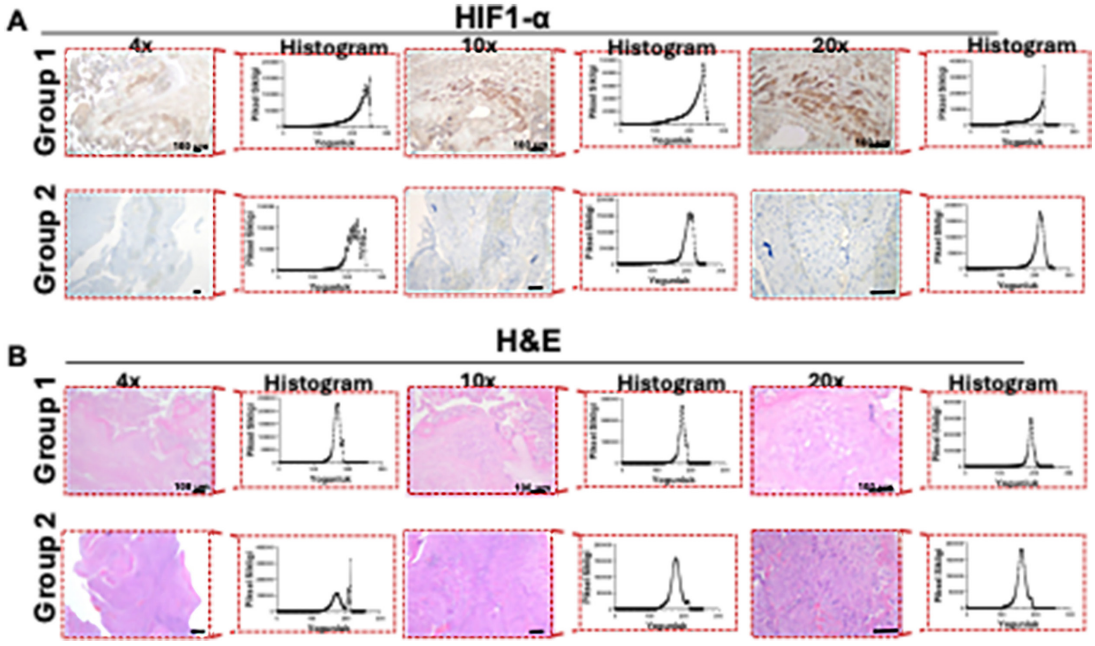

Figure 2. Representative histological images from Group 1 and Group 2. (A) HIF-1α-stained sections and (B) H&E-stained sections at 4×, 10×, and 20× magnifications from pathological specimens (n=58)

HIF1-a: Hypoxia-inducible factor 1-alpha

Table 1. Comparison of demographic variables between the groups

	Group 1 (n=29)	Group 2 (n=29)	*p* value
Age	34.31±3.98	30.44±5.30	0.12
Gravida	4 (2-9)	3 (1-6)	**0.021***
Parity	2 (1-6)	2 (1-4)	**0.016***
Number of previous cesarean deliveries	2 (1-5)	1 (1-4)	**0.010***
BMI (kg/m²)	29.41 (23.53-37.10)	30.12 (23.92-54.69)	0.715
Gestational age at delivery (days)	239 (226-275) (34 weeks 1 day)	272 (247-278) (38 weeks 6 days)	**<0.001***
Presence of comorbidities n (%)	8 (27.58)	7 (24.13)	0.38
Birth weight (g)	2413 (1740-3835)	3250 (2480-3750)	**<0.001***

*Statistically significant
BMI: Body mass index

Qualitative evaluation of HIF-1α antibody staining intensities is shown in Table 2. None of the patients in Group 1 had a score of zero for staining, whereas tissue samples of 13 patients (44.8%) in Group 2 did not exhibit any staining for HIF-1α. Mild staining (staining intensity 1) was observed in seven (24.13%) of Group 1 and in 15 patients (51.72%) in Group 2. Moderate staining (score 2) was reported in nine patients (31.03%) in Group 1 and in 1 patient (3.45%) in Group 2. Strong staining (staining intensity 3) was observed in 13 patients (44.82%) in Group 1, while none of the patients in Group 2 exhibited strong staining. There was a significant difference in the distribution of staining intensities between the two groups ($p<0.001$). Furthermore, the Mantel-Haenszel test for trend demonstrated a significant trend across the ordered staining categories, indicating that Group 1 had a higher proportion of cases with intense staining compared to Group 2 ($p<0.001$).

Furthermore, among the patients in Group 1, 15 (52%) patients underwent total abdominal hysterectomy, 13 (45%) patients underwent supracervical hysterectomy, and 1 (3.45%) patient underwent segmental resection. FIGO PAS staging for Group 1 showed nine patients as stage 2 (31%), 9 as stage 3A (31%), 10 as stage 3B (35%), and 1 as stage 3C (3.45%). Staging was determined based on both preoperative ultrasound imaging and final pathology reports. FIGO staging of PAS is as follows: stage 1 abnormal adherent placenta; stage 2 abnormal invasive placenta, increta; stage 3 abnormal invasive placenta, percreta; subdivided into stage 3A placenta limited to uterine serosa; stage 3B bladder invasion; stage 3C placenta involving pelvic wall.[12]

Quantitative Comparison of HIF-1α Staining Between Groups

The percentage positive staining area of HIF-1α expression, was significantly greater in Group 1 (73.95% ±8.21) compared to Group 2 (65.78% ±7.66) ($p<0.001$) (Figure 3A). The normalized average positive region area was also significantly higher in Group 1 (0.14±0.07) than in Group 2 (0.11±0.05) ($p=0.044$) (Figure 3B). The total number of positive regions was 611.41±263.88 in Group 1 and 777.44±432.11 in Group 2 ($p=0.082$) (Figure 3C). The similar number of positive regions observed in both groups suggest that, despite significant differences in the size and distribution of these regions, their overall frequency remained comparable.

The average positive region area differed significantly between the groups: Group 1 had a larger mean positive area (7834.21±3976.79 pixels) compared to Group 2 (5565.17±3172.82 pixels) ($p=0.019$) (Figure 3D). The normalized mean intensity after grey-scale conversion was 73.58±3.82 in Group 1 and 72.38±3.20 in Group 2 ($p=0.201$) (Figure 3E).

The comparison of positive staining area (%), normalized average positive region area (%), total number of positive regions (pixels), average positive region area (pixels), and normalized mean intensity between the groups, along with the corresponding p values, is summarized in Table 3.

Table 2. Qualitative evaluation of HIF-1α antibody staining intensities

Staining intensity, n (%)	Group 1 (n=29)	Group 2 (n=29)
Staining intensity 0	0 (0)	13 (44.8)
Staining intensity 1	7 (24.13)	15 (51.72)
Staining intensity 2	9 (31.03)	1 (3.45)
Staining intensity 3	13 (44.82)	0 (0)
p value*	<0.001	
Trend p value+	<0.001	

*Pearson's chi-square test for overall distribution, +Linear-by-linear association test (Mantel-Haenszel test for trend)

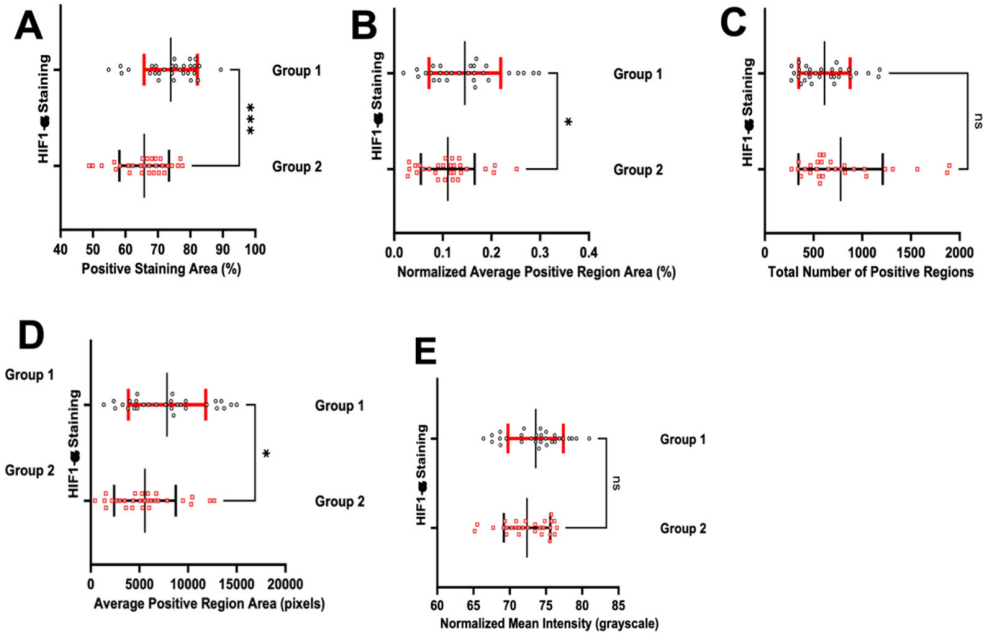

Figure 3. Quantitative comparison of HIF-1α staining between groups. (A) Positive staining area (%), (B) normalized average positive region area, (C) total number of positive regions, (D) average positive region area, (E) average grayscale intensity

HIF1-a: Hypoxia-inducible factor 1-alpha

Table 3. Comparison of quantitative analysis of HIF-1α staining between Group 1 and Group

	Group 1 (n=29)	Group 2 (n=29)	p value
Positive staining area (%)	73.95±8.21	65.78±7.66	**<0.001***
Normalized average positive region area (%)	0.14±0.07	0.11±0.05	**0.044***
Total number of positive regions (pixels)	611.41±263.88	777.44±432.11	0.082
Average positive region area (pixels)	7834.21±3976.79	5565.17±3172.82	**0.019***
Normalized mean intensity (grayscale)	73.58±3.82	72.38±3.20	0.201

*Statistically significant

DISCUSSION

In our study, increased HIF-1α expression in Group 1 as demonstrated by the percentage of positively stained area, normalized average positive region area, and average positive region area all being significantly greater in Group 1 compared to Group 2. The absence of a significant difference in mean intensity suggests that while the extent and distribution of expression varied, the overall presence of HIF-1α remained similar across the groups. Furthermore, the lack of a significant difference in the total number of positive regions between the groups may reflect increased tissue heterogeneity in the microenvironment of Group 1.

Hypoxia plays an important role in the pathogenesis of PAS. Two key studies have investigated the role of HIF-1α in PAS. The first by Yan et al.[13] in 2020 included 10 PAS cases, 20 cases with placenta previa, and 30 healthy pregnancies. In their real-time polymerase chain reaction analysis of placental tissue, HIF-1α expression was significantly greater in the placentas of PAS group compared to the placenta previa and healthy control groups. Their sampling primarily reflected increased HIF-1α expression in trophoblastic cells. In contrast, our study evaluated HIF-1α expression in decidual tissue, which is considered the primary site of abnormal trophoblast invasion. Previous endometrial interventions may result in impaired decidual remodeling and localized hypoxia, thereby increasing HIF-1α expression and potentially leading to abnormal trophoblast invasion. Therefore, we suggest that trophoblastic cellular hypoxia may be the result of hypoxia in the decidual tissue.

The second study addressing the role of HIF-1α in PAS pathogenesis was carried out by Chen et al.[14] and included 10 PAS cases and 10 healthy pregnancies. Placental samples from both groups were analyzed using immunohistochemistry for hypoxia-induced autophagy markers (HIF-1α, Beclin 1, LC3B, and P62) and invasion-related markers (E-cadherin and MMP-9). These authors found higher HIF-1α expression in trophoblasts from PAS cases than in controls and proposed that chronic hypoxia may contribute to PAS development by disrupting autophagic mechanisms and enhancing trophoblastic invasiveness. Notably, this study also focused on trophoblasts rather than decidual tissue, a methodological contrast to our approach.

Another study examining the association between PAS and proangiogenic mediators included 16 PAS cases, 31 with placenta previa, and 6 healthy pregnancies.[15] IHC analysis revealed increased VEGF expression in the placentas of PAS patients, whereas expression of endostatin (a VEGF antagonist) and the angiogenesis inhibitor, endoglin, was decreased. This study compared invasive placental tissue with decidual tissue from healthy controls, a methodological choice that might explain differing results compared to previous studies focused on trophoblastic HIF-1α expression.

Normal and pathological angiogenesis are regulated by various mediators, with HIF-1α playing a central role. Angiogenesis is typically triggered by stimuli such as hypoxia, ischemia, or vascular injury, which in turn upregulate the expression of proangiogenic growth factors.[16] HIF-1α, as a key transcription factor, orchestrates the expression of numerous genes involved in angiogenesis, glucose metabolism, and cell proliferation. Among the target genes for HIF-1α is VEGF, which is critical for both the initiation and maintenance of angiogenesis and is regulated at every stage by HIF-1α.[17,18]

The relationship between hypoxia-induced HIF-1α overactivation and abnormal vascularization is perhaps best exemplified in tumor biology. As tumor cells proliferate rapidly, the balance between oxygen supply and demand is disrupted, triggering HIF-1α-mediated upregulation of proangiogenic factors.[19] Elevated HIF-1α expression has been documented in several cancers, including breast, liver, thymus, cervix, and kidney malignancies. HIF-1α is thus considered a potential therapeutic target in conditions such as ischemic diseases and cancer, where activation or inhibition is desired, respectively. Given the tumor-like invasive behavior of PAS, anti-HIF-1α therapies may hold promise as a potential treatment or prophylactic strategy.

Study Limitations

The primary limitation of our study is the significant difference in gestational age at delivery between the groups. While elective CS delivery was performed at around 34 weeks in PAS patients according to standard recommendations of American College of Obstetricians and Gynecologists,[20] control subjects delivering at similar gestational ages typically did so due to underlying placental pathologies such as preeclampsia or fetal growth restriction. Therefore, term pregnancies were included in the control group. A further limitation of this study is the lack of adjustment for potential confounding factors, such as placental location, number of prior CS deliveries, and maternal comorbidities, which may have influenced HIF-1α expression levels. Furthermore, patients with low lying placentas were not included as a third group. Given that all PAS patients had low-lying placentas while none of the control patients did, the inclusion of a hypothetical third group with low-lying placentas could have enabled a clearer assessment of whether HIF-1 alpha expression is associated with placental location.

One of the main strengths of our study lies in the IHC evaluation of HIF-1α in decidual tissue. Most published studies have assessed HIF-1α expression in trophoblasts. However, from a pathophysiological perspective, it is more plausible that hypoxia within the decidua upregulates proangiogenic mediators like VEGF, thereby facilitating abnormal trophoblast invasion. Furthermore, the well-documented absence or disruption of Nitabuch's layer in PAS supports the hypothesis of a hypoxic microenvironment in this region. Guan et al.[21] focused on the role of HIF-1α in hepatic fibrosis and indicated that HIF-1α expression was increased before the fibrosis develops and inhibition of HIF-1α may suppress the fibrosis.[21] This finding supports the hypothesis that improper regeneration of Nitabuch's layer may be due to increased HIF-1α levels in uterine scarring.

CONCLUSION

In conclusion, the aim was to investigate the pathogenesis of PAS by investigating the role of HIF-1α in abnormal trophoblastic invasion. We found that HIF-1α expression was significantly increased in decidual tissue of patients diagnosed with PAS compared to those with a history of prior CS. This finding supports our hypothesis that hypoxic conditions may arise in structurally compromised decidua because of previous CS deliveries and/or endometrial interventions, subsequently promoting the expression of proangiogenic factors. Future studies with larger patient cohorts, including pregnancies affected by low-lying placentas, may further clarify the association between HIF-1α and the abnormal trophoblastic invasion and vascularization observed in PAS.

Ethics

Ethics Committee Approval: The research was granted ethical approval by the Ethics Committee of Başaksehir Çam and Sakura City Hospital (protocol number: KAEK-11/14.08.2024.103, date: 19.08.2024)

Informed Consent: The privacy rights of human subjects have been observed and that informed consent was obtained for experimentation with human subjects.

Footnotes

Authorship Contributions

Surgical and Medical Practices: R.A.B., S.A., B.Y., Concept: B.Y., Design: V.A., H.E., B.Y., Data Collection or Processing: R.A.B., S.A., Ş.K.D., Analysis or Interpretation: R.A.B., S.A., Ş.K.D., İ.D.D., B.Y., Literature Search: R.A.B., T.Y.B., O.M.G., V.A., H.E., Writing: R.A.B., T.Y.B., O.M.G., B.Y.

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

Financial Disclosure: The authors declared that this study received no financial support.

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