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Impact of abnormal placentation on the risk of hypertensive disorders in pregnancy: A retrospective analysis

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Abstract

We aimed to investigate the impact of abnormal placental location and placenta accreta spectrum (PAS) disorders on the incidence of hypertensive disorders of pregnancy. This retrospective, single-center study was conducted at a tertiary maternity hospital between 2018 and 2022. The study population was classified according to abnormal placentation, including control (normal placentation), low-lying placenta (LP), placenta previa (PP), and PAS. The PAS group was further divided into subtypes: accreta, increta, percreta. Logistic regression analysis was performed to evaluate factors influencing the incidence of HDPs and pregnancy-induced hypertension (PIH) and their association with abnormal placentation and PAS subtypes. A total of 337 pregnant women were recruited into the study, with 222 abnormal placentations (85 were classified as LP, 72 as PP and 65 as PAS) and 155 controls. Among the participants, 37 women (9.81%) were diagnosed with HDPs. The incidence of HDPs was significantly lower in the PP (4.2%) and PAS (7.7%) groups compared to the control group (12.3%) ($p<0.001$). The prevalence rates of HDPs were 10.3% in women without PAS, 11.1% with accreta, 8.7% with increta, and 4.1% with percreta ($p<0.001$). For PIH, the prevalence rates were 7.4% without PAS, 5.6% with accreta, 4.3% with increta, and 0% with percreta ($p<0.001$). After adjustment for confounders, including advanced maternal age, nulliparity, gestational diabetes mellitus (GDM), and elevated thyroid-stimulating hormone (TSH) levels, a significant negative association was observed between PP and the risk of PIH (OR=0.215, 95% CI: 0.128–1.243, p=0.001) and HDPs (OR=0.215, 95% CI: 0.128–1.243, p=0.001). Similarly, a negative association was observed between PAS and the risk of PIH (OR=0.550, 95% CI: 0.295–1.120, p=0.004) and HDPs (OR=0.610, 95% CI: 0.350–1.320, p=0.004). However, no association was found between HDPs and LP. Abnormal placentation, particularly PP and PAS, is associated with a reduced risk of HDPs, suggesting a potential protective effect. Additionally, the prevalence of HDPs decreases as the invasiveness of PAS increases.

Keywords: Hypertensive disorders of pregnancy, abnormal placental location, placenta previa, placenta accreta spectrum disorders

Introduction

Hypertensive disorders of pregnancy (HDPs) represent a significant global cause of maternal and perinatal morbidity and mortality, affecting approximately 6-8% of pregnancies, especially in low- to middle-income countries [1]. Several factors, including advanced maternal age (over 40 years), pre-pregnancy obesity, excessive gestational weight gain, and all types of glucose intolerance, are associated with an increased risk of HDPs [2]. HDPs are classified into four categories including chronic hypertension, gestational hypertension, preeclampsia-eclampsia, and preeclampsia superimposed on chronic hypertension [3]. Gestational hypertension and preeclampsia-eclampsia are collectively referred to as pregnancy-induced hypertension (PIH), which typically occurs after the 20th week of gestation [4].

Preeclampsia alone is responsible for approximately 70,000 maternal and 500,000 fetal deaths globally each year [5]. Despite the profound impact of preeclampsia, its pathophysiology remains poorly understood [6]. Increasing evidence suggests that the placenta, rather than the fetus, plays a central role in the development of preeclampsia, with the delivery of the placenta being the most effective treatment [7].

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In preeclampsia, the invasive capacity of extravillous trophoblasts (EVT) is impaired compared to normal pregnancies, leading to insufficient spiral artery remodeling, reduced uteroplacental blood flow, placental hypoxia, maternal endothelial damage, and associated clinical symptoms [2]. Conversely, in placenta accreta spectrum (PAS) disorders, EVT invades deeply into the uterine tissue, replacing decidual and myometrial structures [8].

The relationship between PAS and HDPs remains controversial. Some studies have reported a positive association between HDPs and the occurrence of PAS [9], whereas others have found no significant association [10,11]. Additionally, a meta-analysis suggested that HDPs may be significantly associated with a lower prevalence of PAS [12]. PAS is frequently associated with placenta previa (PP), and recent evidence suggests that PP may be associated with a reduced incidence of preeclampsia and lower maternal blood pressure [13,14]. While some studies have reported a protective effect of PP [15,16], others have found no significant association [17] or even an increased incidence [18].

In our country, hypertensive disorders rank as the second leading cause of maternal mortality after hemorrhage, with a prevalence of 26.1% [19]. Furthermore, the rising rate of cesarean sections has contributed to an increase in cases of PAS, which in turn leads to severe hemorrhage and increased risk of maternal morbidity and mortality. Despite these critical observations, the mechanisms by which placental abnormalities contribute to the development of HDPs remain the subject of ongoing debate.

In this study, we aimed to investigate the incidence and potential risk factors for HDPs in patients with abnormal placental location and/or PAS at a tertiary maternity hospital.

Material and Methods

Study Population

This retrospective case-control study was conducted at a tertiary maternity hospital for high-risk pregnancies. The study population consisted of women aged 18-45 years with singleton pregnancies who delivered at our institution between January 2020 and December 2022. Exclusion criteria included multiple pregnancies, gestational age <28 weeks, a history of PIH, pregestational diabetes, liver or kidney dysfunction, autoimmune diseases, conception via in vitro fertilization, and incomplete clinical or delivery data.

Data Collection

Clinical and pathological data were collected from the hospital electronic database and medical records, including maternal age, body mass index (BMI), gestational age at delivery, gravidity, placental location (normal, low-lying placenta (LP) or PP), PAS disorders (accreta, increta, percreta), gestational diabetes mellitus (GDM), thyroid-stimulating hormone (TSH) levels, and HDPs. Prenatal diagnostic assessments were performed using a 3D ultrasound system (GE Voluson E6, GE Medical Systems, Zipf, Austria), with all examinations were performed by a maternal-fetal medicine specialist experienced in the diagnosis of PAS and conducting related surgery.

Diagnosis of Placenta Previa

The distance between the internal cervical os and the placental edge was measured by vaginal ultrasound at 32 weeks of gestation and repeated three weeks later. PP was diagnosed when placental tissue covered the internal cervical os. If the placental edge was ≤20 mm from the internal os without covering it, the condition was classified as LP. The diagnosis was confirmed during labor [20].

Diagnosis of Placenta Accreta Spectrum Disorders

PAS was diagnosed in accordance with the International Federation of Gynaecology and Obstetrics (FIGO) guidelines [21], based on clinical evidence of placental invasion observed at delivery and/or histological examination of hysterectomy specimens, with three subtypes classified as FIGO grade 1 (accreta), FIGO grade 2 (increta) or FIGO grade 3 (percreta). FIGO grade 1 was clinically diagnosed if the placenta failed to detach despite the use of synthetic oxytocin and gentle controlled cord traction, requiring mechanical or surgical intervention due to severe hemorrhage from the implantation site during manual removal attempts.

Diagnosis of Hypertensive Disorders of Pregnancy

Gestational hypertension was defined as a blood pressure of ≥140/90 mmHg on two occasions, measured at least 4 hours apart, occurring after 20 weeks of gestation in a previously normotensive woman [22]. Pre-eclampsia, with or without severe features, was diagnosed by a new-onset of blood pressure of ≥140/90 mmHg on two occasions at least 4 hours apart after 20 weeks' gestation in a previously normotensive woman with proteinuria (urinary total protein/creatinine ratio >30 or <300 mg in 24 hours) [22].

Data Analysis

Continuous variables were presented as mean and range (minimum–maximum) or mean±standard deviation, depending on their distribution. Categorical variables were expressed as frequencies and percentages, reported as numbers (n) and percentages (%). Differences in HDPs between groups were analyzed using descriptive statistics, with either chi-square tests or Fisher's exact tests as appropriate. Logistic regression analysis was used to estimate odds ratio (OR) with 95% confidence interval (CI) to identify factors influencing the incidence of HDPs and PIH. All statistical analyses were performed using SPSS Statistics, version 26 (SPSS Inc., Chicago, IL, USA). A p-value of <0.05 was considered statistically significant.

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Ethical Consideration

The study was conducted in accordance with the principles of the Declaration of Helsinki and received ethical approval from the Ethics Committee of Etlik Zubeyde Hanim Women's Health Care, Training and Research Hospital, University of Heath Science, (approval number: 21.04.22-05/31). Given the retrospective nature of the study, informed consent was waived with the approval of the local ethics committee.

Results

Between 2018 and 2022, a total of 63,850 deliveries were performed at our institution, of which 377 patients met the inclusion criteria for this study. Among these, 222 had an abnormal placental location: 85 were classified as LP, 72 as PP, and 65 as PAS. The remaining 155 patients constituted the control group. The demographic characteristics of the study population are shown in Table 1. Compared with the control group, patients in the PAS group were older, had higher parity, and had a lower incidence of GDM, lower TSH levels, earlier gestational age at delivery (p<0.001). In addition, although the PAS group exhibited a lower birth weight (p<0.045), the incidence of fetal growth restriction was not increased. The study population included 37 (%9.8) patients diagnosed with HDPs (Table 2). The incidence of HDPs across the groups was 12.3% (19/155) in the control group, 11.8% (10/85) in the LP group, 4.2% (3/72) in the PP group, and 7.7% (5/65) in the PAS group. HDPs were significantly lower in the PP and PAS groups compared with the control group (p<0.001).

Table 1. The demographic characteristics of the study population

Patient's characteristics	Control (n=155)	Low-lying placenta (n=85)	Placenta previa (n=72)	Placenta accreta (n=65)	p value
Age (years)					
20-34	139 (89.6%)	71 (83.5%)	56 (77.7%)	40 (61.5%)	<0.001
≥35	16(10.4%)	14 (16.5%)	16 (22.3%)	25 (38.5%)	
BMI (kg/m²)	27.40 (20-44)	25.82 (24-34)	25.32 (19-32)	28.42 (22-50)	0.253
Parity (%)					
Nulliparous	61 (39.3%)	20 (23.5%)	6 (8.3%)	1 (1.5%)	<0.001
Multiparous	39 (60.7%)	65 (76.5%)	66 (91.7%)	64 (98.5%)	
GDM (%)	27 (17.4%)	11 (12.9%)	6 (8.3%)	5 (7.7%)	<0.001
TSH (mIU/L)	2.12 (1.4-2.5)	1.8 (1.1-2.1)	1.5 (0.9-1.8)	1.1 (0.5-1.3)	<0.001
Gestational age (weeks)	39.1±3.25	38.2±2.95	36.5±2.12	35.8±1.79	<0.001
Birth weight (g)	3370±475	3160±700	2965±550	2450±350	0.04

BMI: body mass index, GDM: gestational diabetes mellitus, TSH: thyroid-stimulating hormone

Table 2. Incidence of hypertensive disorders of pregnancy in the study population (%)

Variables	Control (n=155)	Low-lying placenta (n=85)	Placenta previa (n=72)	Placenta accreta (n=65)	p value
Gestational hypertension	6 (3.87)	3 (3.53)	1 (1.39)	1 (1.54)	<0.001
Preeclampsia	8 (5.16)	4 (4.71)	1 (1.39)	1 (1.54)	<0.001
Chronic hypertension	2 (1.29)	2 (2.35)	1 (1.39)	3 (6.15)	0.785
Chronic hypertension+preeclampsia	3 (1.94)	1 (1.17)	0	0	<0.001

Logistic regression analysis was performed to evaluate the factors influencing the incidence of HDPs (Table 3). The results showed that the risk of HDPs increased with age; specifically, patients aged ≥35 years had a higher risk of HDPs compared to those aged 20-34 years (OR=1.537, 95% CI: 1.230-2.690, p=0.005). GDM (OR=2.187, 95% CI: 0.915–5.654, p=0.007), nulliparity (OR=3.210, 95% CI: 2.350–3.778, p=0.001), and higher TSH levels (OR=1.567, 95% CI: 1.285–2.876, p<0.001) were associated with an increased risk of HDPs. In contrast, PP (OR=0.215, 95% CI: 0.128–1.243, p=0.001), PAS (OR=0.610, 95% CI: 0.350-1.320, p=0.046) and gestational age at delivery (OR=0.950, 95% CI: 0.560–1.250, p=0.005) were associated with a reduced risk of HDPs. No significant association was found between HDPs and LP (OR=0.95, 95% CI: 0.82-1.25, p=0.850).

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Table 3. Logistic regression analysis of factors associated with hypertensive disorders of pregnancy in the study population

Variables	OR	95% CI	p value
Age (years)			
20-34	0.625	0.315-1.435	<0.001
≥35	1.537	1.230- 2.690	
BMI (kg/m²)	1.025	0.850-1.235	0.125
Parity (%)			
Nulliparous	3.210	2.350-3.778	<0.001
Multiparous	0.081	0.032-0.520	
GDM (%)	2.187	0.915-5.654	0.007
TSH (mIU/L)	1.725	1.375-2.890	<0.001
Placenta previa	0.311	0.230-0.93	<0.001
Low-lying placenta	0.95	0.82-1.25	0.850
PAS	0.596	0.350-1.320	0.046
Gestational age (weeks)	0.950	0.560-1.250	0.005

PAS: placenta accreta spectrum, BMI: body mass index, GDM: gestational diabetes mellitus, TSH: thyroid-stimulating hormone, OR: odds ratio, CI: confidence interval

After excluding patients with chronic hypertension and pre-eclampsia superimposed on chronic hypertension, the incidence and factors influencing PIH were further analyzed (Table 4). The results showed that the incidence of PIH was significantly lower in the PP (2.8%) and PAS groups (3.1%) than in the control group (9%) (p<0.001). Logistic regression analysis showed a significant reduction in the incidence of PIH associated with multiparity (OR=0.062, 95% CI: 0.035-0.320, p=0.001), PP (OR=0.215, 95% CI: 0.128–1.243, p=0.001) and PAS (OR=0.550, 95% CI: 0.295-1.120, p=0.004). However, no significant association was found between PIH and LP (OR=0.95, 95% CI: 0.452–1.854, p=0.750).

Table 4. Logistic regression analysis of factors associated with pregnancy-induced hypertension in the study population

Variables	OR	95% CI	p value
Age (years)			
20-34	0.515	0.515-1.635	<0.001
≥35	1.587	1.030- 2.790	
BMI (kg/m²)	1.025	0.850-1.235	0.125
Parity (%)			
Nulliparous	3.520	2.650-3.978	<0.001
Multiparous	0.062	0.035-0.320	
GDM (%)	1.985	0.815-5.255	0.006
TSH (mIU/L)	1.567	1.285-2.876	<0.001
Placenta previa	0.215	0.128-1.243	<0.001
Low-lying placenta	0.92	0.452-1.854	0.750
PAS	0.550	0.295-1.120	0.004
Gestational age (weeks)	0.945	0.5450-1.320	0.005

PAS: placenta accreta spectrum, BMI: body mass index, GDM: gestational diabetes mellitus, TSH: thyroid-stimulating hormone, OR: odds ratio; 95% CI, 95% confidence interval.

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To further assess the association between PAS and HDPs, the study population was divided into PAS and non-PAS groups, with additional analysis by PAS subtypes. Patient characteristics were examined for each PAS subtype (Table 5). The prevalence of HDPs was 10.3% (32/312) in patients without PAS, 11.1% (2/18) with accreta, 8.7% (2/23) with increta, and 4.1% (1/24) with percreta. For PIH, the prevalence was 7.4% (23/312) in patients without PAS, 5.6% (1/18) with accreta, 4.3% (1/23) with increta, and 0% with percreta. Logistic regression analysis was performed to determine the odds ratios (ORs) for HDPs and PIH across PAS subgroups. The ORs for HDPs were as follows: accreta versus non-PAS (OR=1.13, 95% CI: 0.72–1.93), increta versus non-PAS (OR=0.86, 95% CI: 0.54–1.34), and percreta versus non-PAS (OR=0.39, 95% CI: 0.42–0.62). For PIH, the ORs were: accreta versus non-PAS (OR=0.74, 95% CI: 0.59–0.85), increta versus non-PAS (OR=0.57, 95% CI: 0.44–0.67), and percreta versus non-PAS (OR=0.25, 95% CI: 0.17–0.34).

Table 5. Incidence of hypertensive disorders of pregnancy and pregnancy-induced hypertension among PAS subtypes and non-PAS group

	Non-PAS group	PAS group				
Variables	**Total (n=312)**	**Total (n=65)**	**Placenta accreta (n=18)**	**Placenta increta (n=23)**	**Placenta percreta (n=24)**	**p value**
Age, ≥35	46 (14.7%)	25 (38.5%)	5 (21.7%)	9 (50%)	11 (45.8%)	<0.001
HDPs	32 (10.3%)	5 (7.7%)	2 (11.1%)	2 (8.7%)	1 (4.1%)	<0.001
PIH	23 (7.4%)	2 (3.1%)	1 (5.6%)	1 (4.3%)	0	0.008
HDPs OR (95% CI)		0.75 (0.64-0.82)	1.13 (0.72-0.93)	0.86 (0.54-0.81	0.39 (0.42-0.62)	<0.001
PIH OR (95% CI)		0.30 (0.21-0.43)	0.74 (0.59-0.85)	0.57 (0.44-0.67)	0.25 (0.17-034)	<0.001

HDPs: hypertensive disorders of pregnancy, PIH: pregnancy-induced hypertension, PAS: placenta accreta spectrum, OR: odds ratio; 95% CI, 95% confidence interval

Discussion

In recent years, the incidence of PP and/or PAS, which may lead to life-threatening hemorrhage and/or peripartum hysterectomy, has gradually increased worldwide due to rising cesarean delivery rates [8]. In addition, hypertension is the most common medical disorder during pregnancy, affecting up to one in ten pregnancies and complicating approximately 10% of pregnancies [3]. Several studies have investigated the association between abnormal placentation and the risk of hypertensive disorders; however, the results have been inconsistent.

In the present study, we observed that patients with abnormal placental location had a significantly lower incidence of HDPs (8.1%) compared to those with normal placental location (12.3%), with the most pronounced reduction seen in cases involving PP with placenta percreta. After adjusting for confounding factors, including advanced maternal age, nulliparity, GDM, and elevated TSH levels, the inverse association between abnormal placental location and HDPs remained.

The inverse relationship between PP and PIH was initially observed by Bienarz [23], who reported a higher frequency of high-seated (fundal and upper segment) placentas in cases of preeclampsia. Lieberman et al. [24] later suggested that improved maternal blood flow in PP, facilitated by the wider isthmic segment of the uterine artery, might explain this protective effect. A meta-analysis by Yin et al. [25] further supported a protective association between PP and HDPs, showing a strong inverse association between PP and PIH, even after controlling for confounding factors such as parity and timing of delivery. Consistent with these findings, our study demonstrated a lower incidence of PIH in patients with PP, suggesting that PP may act as a protective factor. Furthermore, Hasegawa et al. [26] found that low cord insertion, even in the absence of PP, was associated with a lower incidence of preeclampsia and reduced maternal blood pressure. However, our study did not find a significant association between PIH and LP. Previous studies have reported conflicting results regarding the relationship between PP and the incidence of PIH, with some finding no association and others identifying a positive correlation [27,28]. A study by Baumfeld et al. [18] found a positive association between PP and the risk of PIH, suggesting that in cases of PP, abnormal placentation-including shallow cytotrophoblast invasion-may contribute to a higher incidence of preeclampsia.

The discrepancies between previous studies may be due to various factors, such as differences in study populations, sample sizes, and other methodological variations. In addition, pregnancy is a dynamic process, and basic characteristics of pregnant women—such as maternal age, gestational age, and pre-pregnancy BMI—as well as other pregnancy-related factors may influence the occurrence of HDPs.

Successful pregnancy establishment depends on the proper coordination of embryo implantation, placentation, trophoblast invasion, and remodelling of the uterine spiral arteries. Disruption of these processes can lead to complications such as preeclampsia and PAS [29]. Although the exact pathogenesis of preeclampsia remains unclear, reduced interaction between trophoblasts and endometrium/decidua may be a contributing factor. In contrast, the main pathogenesis of PAS is associated with endometrial damage and defective decidualization. Failure of normal decidualization leads to excessive trophoblastic

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invasion, abnormally deep placentation, impaired arterial remodelling, hypoxia, and ischemia.

Usta et al. [9] proposed that hypertension may lead to placenta accreta through endothelial damage or, conversely, that abnormal trophoblast invasion may contribute to hypertension. In contrast, Jauniaux et al. [30] observed that PAS is localized to the scar area, making it unlikely to lead to a systemic disorder such as preeclampsia. Similarly, a meta-analysis by Li et al. [31] showed a lower risk of HDPs in women with PAS, but other studies found no significant association between HDPs and PAS, instead reporting a higher prevalence of hypertension in women without PAS [10,11].

Wang et al. [12] demonstrated that elevated levels of pregnancy-associated plasma protein-A (PAPP-A) are significantly associated with an increased risk of placenta accreta. In contrast, Spencer et al. [32] reported that low PAPP-A levels were associated with an increased risk of pre-eclampsia, particularly in early-onset cases. PAPP-A acts as a protease for syncytiotrophoblast derived insulin-like growth factor binding proteins (IGFBPs). Given the critical role of insulin-like growth factor (IGF) in trophoblast invasion, reduced serum PAPP-A levels may contribute to the increased incidence of pre-eclampsia [33]. Youssef et al. [34] investigated the relationship between first-trimester PAPP-A and soluble fms-like tyrosine kinase-1 (sFlt-1) in pre-eclamptic and normal pregnancies. sFlt-1 is a soluble receptor that irreversibly inhibits vascular endothelial growth factor (VEGF) and placental growth factor (PlGF) by preventing their interaction with endothelial cell receptors, leading to an anti-angiogenic effect and contributing to endothelial dysfunction. This mechanism is implicated a key role in the pathophysiology of preeclampsia, as elevated placental and serum sFlt-1 levels are observed in early pregnancy compared to controls [35]. McMahon et al. [36] showed that invasive placentation is associated with lower levels of sFlt-1 at the maternal-fetal interface, suggesting a critical regulatory role for sFlt-1 in placental invasion. Mei-Tsz Su et al. [37]similarly observed reduced sFlt-1 expression in clinical samples of invasive placentas, further supporting its role in modulating trophoblast invasiveness, which may contribute to the development of preeclampsia. Additionally, aspirin treatment has been shown to reduce sFlt-1 expression in primary placental cells, and sFlt-1 has been found to inhibit both trophoblast invasion and matrix metalloproteinase-2/9 (MMP-2/9) expression, providing further insights into its role in the pathogenesis of preeclampsia [37]. These data suggest that the trend toward a reduction in the incidence of HDPs may be more pronounced when both PP and PAS disorders are present. Consistent with previous studies, our study found that PAS was significantly associated with a lower incidence of HDPs.

Furthermore, Alessandrini et al. [38] showed that with increasing FIGO grades, PLGF levels increase while sFlt-1 expression decreases, with PAS grade 3 cases having the highest PLGF and lowest sFlt-1 levels. Matsuzaki et al. [39] in a study of over 2.7 million women, reported different rates of HDPs by PAS grade, with a HDPs prevalence of 14.2% without PAS, 12.5% with placenta accreta, 8.5% with placenta increta, and 7.5% with placenta percreta. Consistent with these findings, the prevalence of HDPs in our study was 10.3% in women without PAS, 11.1% with accreta, 8.7% with increta, and 4.1% with percreta. For PIH, the rates were 7.4% in women without PAS, 5.6% with accreta, 4.3% with increta, and 0% with percreta. These results suggest that the prevalence of HDPs and PIH decreases as the invasiveness of PAS increases.

Limitations

Despite the significant findings of this study, several limitations must be acknowledged. First, the retrospective design may introduce biases related to data collection and patient selection, which may affect the generalisability of the results. Second, although the sample size is substantial, it may be underpowered to detect subtle differences in outcomes between different degrees of placental abnormality. Third, potential confounding factors, including socioeconomic status and lifestyle choices, which may influence the incidence of HDPs, were not comprehensively assessed. Furthermore, the length of pregnancy is an important characteristic in the examination of HDPs; therefore, future prospective studies adjusting for confounding factors, particularly gestational age at delivery, are warranted.

Conclusion

Abnormal placental location, particularly PP and placenta accreta, was associated with a lower incidence of HDPs, suggesting a potential protective effect. Our findings were further consistent with previous literature indicating an inverse relationship between the invasiveness of placenta accreta and the prevalence of HDPs. These findings contribute to the understanding of the relationship between placental abnormalities and hypertensive disorders and highlight the importance of individualized management strategies for patients with abnormal placentation.

Conflict of Interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical Approval
The study was conducted in accordance with the principles of the Declaration of Helsinki and received ethical approval from the Ethics Committee of Etlik Zubeyde Hanim Gynecology Training and Research Hospital (approval number: 21.04.22-05/31). Given the retrospective nature of the study, informed consent was waived with the approval of the local ethics committee.

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