

Original Research

Effects of Abnormal Placental Location and Placenta Accreta Spectrum Disorder on the Risk of Hypertensive Disorders of Pregnancy

Huijun Liu¹, Xietong Wang^{1,2,*}¹Department of Obstetrics, Shandong Provincial Hospital Affiliated to Shandong University, 250001 Jinan, Shandong, China²Key Laboratory of Birth Regulation and Control Technology of National Health Commission of China, Shandong Provincial Maternal and Child Health Care Hospital Affiliated to Shandong University, 250001 Jinan, Shandong, China*Correspondence: wangxtrep@126.com (Xietong Wang)

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Abstract

Background: This study aimed to investigate the effects of abnormal placental location and placenta accreta spectrum (PAS) disorder on the risk of hypertensive disorders of pregnancy (HDPs). **Methods:** This retrospective study included 985 patients with abnormal placental location and 2100 patients with normal placental location. The incidence of HDPs in patients with abnormal placental location and in those with concurrent abnormal placental location and PAS disorders was analyzed. The factors affecting the incidence of HDPs and pregnancy-induced hypertension (PIH) were analyzed using logistic regression analyses. **Results:** The incidence of HDPs in patients with abnormal placental location (3.55%) was significantly lower than those with normal location (8.23%) ($p < 0.001$). The incidence of HDPs in the placenta previa subgroup (2.87%) was significantly lower than the low-lying placenta subgroup (6.48%) ($p = 0.017$). By including confounding factors (maternal age, gestational age, gravidity, parity, PAS disorders, and gestational diabetes mellitus), the incidence of HDPs (OR (95% CI) = 0.252 (0.149, 0.426), $p < 0.001$) or PIH (OR (95% CI) = 0.294 (0.169, 0.511), $p < 0.001$) was negatively correlated with abnormal placental location. Subgroup analysis revealed that the incidence of HDPs of the PAS subgroup (2.66%) was significantly lower than that of the non-PAS subgroup (5.22%). However, PAS disorder (OR (95% CI) = 0.551 (0.242, 1.254), $p = 0.156$) was not an independent factor of the incidence of HDPs. **Conclusions:** Abnormal placental location could decrease the incidence of HDPs. It was an independent protective factor of HDPs, especially PIH, but PAS disorder was not.

Keywords: abnormal placental location; hypertensive disorders of pregnancy; placenta accreta spectrum disorder; preeclampsia

1. Introduction

Hypertensive disorders of pregnancy (HDPs) are a significant cause of maternal mortality and morbidity worldwide, affecting about 5–10% of all pregnancies [1]. HDPs are classified into four categories including chronic hypertension, chronic hypertension with superimposed preeclampsia, gestational hypertension, and preeclampsia-eclampsia [2,3]. Pregnancy-induced hypertension (PIH) is a subgroup of HDPs, which is defined as hypertension that occurs in pregnancy for the first time after 20 weeks of gestation and disappears following delivery [4] and includes gestational hypertension and preeclampsia-eclampsia [5]. Women with HDPs have on average a twofold higher risk to develop cardiovascular disease later in life in comparison with those with normotensive pregnancies [6].

Preeclampsia, in particular, is one of the most feared complications of pregnancy, characterized by new-onset hypertension, proteinuria and multi-system dysfunction [7, 8].

Accumulating evidence has revealed that the placenta plays an important role in the pathogenesis of preeclampsia [9–11]. A retrospective case-control study has revealed that placenta previa is a significant protective factor of

preeclampsia [12]. A meta-analysis based on 7 cohort studies also demonstrates that the risk of HDPs is reduced in women with placenta previa compared with those with normally implanted placenta [13]. In addition, placenta accreta spectrum (PAS) disorder is a condition characterized by abnormal implantation of the placenta into the uterine myometrium [14]. PAS disorder often occurs together with placenta previa, which is also an obstetric complication associated with high maternal morbidity [15]. However, the association between PAS disorder and HDPs is highly controversial. Usta *et al.* [16] demonstrated that there were positive association between HDPs and placental accreta. Bowman *et al.* [17] revealed that women without placenta accreta had a trend toward more hypertension, and a meta-analysis revealed HDPs was remarkably associated with the reduction of placenta accreta [18]. The mechanism of placental abnormalities in the development of HDPs, especially preeclampsia, remains unclear, and whether it is the influence of abnormal placental location or PAS disorders is controversial.

In the present study, patients were grouped based on placenta location. By combined with a large number of cases of PAS disorders in our hospital, we analyzed the incidence and influencing factors of HDPs in patients with



abnormal placental location or in those with PAS disorders. Our findings will provide a new insight for better understanding of the association between HDPs and abnormal placenta location or PAS disorders.

2. Materials and Methods

2.1 Patients

This retrospective single-center study included women having singleton pregnancies with childbirth who were discharged from our hospital between January 1, 2017 and December 31, 2019. The diagnostic criteria for abnormal placental location and HDPs referred to the 9th edition of Obstetrics and Gynecology [19]. The diagnostic criteria for PAS disorders referred to the FIGO consensus guidelines for placenta accreta spectrum disorders (2018), and PAS disorders included three subtypes: adherent placenta accreta, increta and percreta. A total of 985 patients with abnormal placental location were included in the observation group, which were diagnosed with abnormal placental location by B-ultrasound before delivery or confirmed during operation. The inclusion criteria were as follows: (1) gestation age ≥ 28 weeks and childbirth; and (2) abnormal placental location was confirmed by the last B-ultrasound before termination of pregnancy or intraoperative clinical findings, including low-lying placenta (the distance between the lower edge of the placenta and the intracervical mouth was less than 2 cm, and the lower edge of the placenta reached the intracervical mouth) and placenta previa (the intracervical mouth was partially or completely covered by the lower edge of the placenta). In addition, 2100 randomly selected patients with the last digit of the hospitalization number being 7 were included in the control group. The inclusion criteria were (1) gestation age ≥ 28 weeks and childbirth; and (2) no abnormal placental location was observed by the B-ultrasound and clinical findings. The exclusion criteria for all patients were: (1) previous history of PIH, including gestational hypertension and preeclampsia; (2) patients with chronic diseases during pregnancy, including kidney disease, pregestational diabetes mellitus (PGDM) and insulin-requiring GDM, autoimmune diseases such as systemic lupus erythematosus, antiphospholipid syndrome, and thromboembolism; (3) multiple pregnancies; and (4) gestation age < 28 weeks.

2.2 Data Collection

Clinical and pathologic features were collected, including maternal age, body mass index (BMI), gestational age at delivery, gravidity, parity, PAS disorders (accreta and increta including increta and percreta), gestational diabetes mellitus (GDM), and HDPs.

2.3 Statistical Analysis

All statistical analyses were performed using SPSS software (version 25.0, SPSS Inc., Chicago, IL, USA).

Comparisons of continuous data were conducted by t test and Wilcoxon rank-sum test for normal and nonnormal distribution data, respectively. Categorical variables were analyzed using Chi-square (χ^2) test or corrected χ^2 test. To assess the factors affecting the incidence of HDPs, logistic regression analyses were conducted to estimate odds ratio (OR) with 95% confidence interval (CI), and the adjusted confounding factors included maternal age, gestational age, gravidity, parity, PAS disorders, and GDM. $p < 0.05$ was regarded as statistically significant.

3. Results

3.1 Baseline Characteristics of Patients

A total of 985 patients with abnormal placental location were enrolled in the observation group, and 2100 patients were included in the control group. The baseline characteristics of patients are shown in Table 1. As results, there were statistically significant differences between the observation group and the control group in age, gestational age at delivery, gravidity, parity, PAS disorders, and GDM (all $p < 0.001$). Compared to the control group, the observation group demonstrated older maternal age, fewer weeks of gestational age at delivery, higher frequency of gravidity, higher frequency of parity, higher incidence of PAS disorders, and lower incidence of GDM. However, the two groups had no significant difference in BMI.

3.2 The Incidence and Factors of HDPs

The HDPs occurred in 173 patients in the control group and 35 patients in the observation group, with the incidence of 8.23% and 3.55%, respectively. The incidence of HDPs of the observation group was significantly lower than that of the control group ($\chi^2 = 23.40$, $p < 0.001$) (Table 2). The incidence of HDPs in the placenta previa subgroup [2.87% (23/800)] was also significantly lower than that in the low-lying placenta subgroup [6.48% (12/185)] ($\chi^2 = 5.72$, $p = 0.017$).

Logistic regression analysis was then performed to analyze the factors affecting the incidence of HDPs. The results showed that the incidence of HDPs was positively correlated with maternal age (OR (95% CI) = 1.051 (1.015, 1.089), $p = 0.005$) and GDM (OR (95% CI) = 1.608 (1.132, 2.286), $p = 0.008$), while negatively correlated with gestational age at delivery (OR (95% CI) = 0.712 (0.678, 0.748), $p < 0.001$) and abnormal placental location (OR (95% CI) = 0.252 (0.149, 0.426), $p < 0.001$) (Table 3). Abnormal placental location might be a protective factor of HDPs.

In addition, the incidence and influencing factors of PIH was further analyzed after excluding the patients with chronic hypertension and chronic hypertension with superimposed preeclampsia. The results showed that the incidence of PIH of the observation group (2.96%) was significantly lower than that of the control group (7.00%) ($\chi^2 = 20.14$, $p < 0.001$). Further logistic regression analysis revealed that the incidence of PIH was significantly associ-

Table 1. Baseline characteristics of all included patients.

Groups/Characteristics	Age (years)	Gestational age (weeks)	BMI	Gravidity (%)					Parity (%)				PAS (%)		GDM (%)
	[Mean \pm SD]	[Median (p25, p75)]		G1	G2	G3	G4	\geq G5	P1	P2	P3	P4	Accreta	Increta	
Control group (n = 2100)	31.07 \pm 4.55	39 (38, 39.75)	28.16 \pm 3.86	696 (33.14)	674 (32.10)	416 (19.81)	212 (10.10)	102 (4.85)	979 (46.62)	1018 (48.48)	97 (4.62)	6 (0.29)	18 (0.86)	8 (0.38)	437 (20.81)
Observation group (n = 985)	32.90 \pm 4.80	36 (35, 37)	27.88 \pm 3.52	71 (7.21)	225 (22.84)	266 (27.01)	219 (22.23)	204 (20.71)	145 (14.73)	647 (65.69)	183 (18.58)	10 (0.10)	46 (4.57)	595 (60.40)	143 (14.52)
Low-lying placenta subgroup (n = 185)	32.81 \pm 4.85	37 (35, 38)	28.00 \pm 3.53	25 (13.51)	37 (20.00)	52 (28.11)	44 (23.78)	27 (14.60)	46 (24.86)	124 (67.03)	15 (8.11)	0 (0.00)	13 (7.03)	54 (29.19)	31 (16.76)
Placenta previa sub-group (n = 800)	32.92 \pm 4.82	36 (35, 37)	27.86 \pm 3.52	46 (5.75)	188 (23.50)	214 (26.75)	175 (21.88)	177 (22.12)	99 (12.38)	523 (65.38)	168 (21.00)	10 (1.25)	32 (4.00)	541 (67.63)	112 (14.00)
t/Z/ χ^2	-9.988	-31.10	1.86	-21.094					-19.212				1609.08		17.39
p value	<0.001	<0.001	0.063	<0.001					<0.001				<0.001		<0.001

BMI, body mass index; PAS, placenta accreta spectrum; GDM, gestational diabetes mellitus.

Table 2. The incidence of hypertensive disorders of pregnancy in each group of patients (%).

	Chronic hypertension	Chronic hypertension with superimposed preeclampsia	Gestational hypertension	Preeclampsia
Control group (n = 2100)	11 (0.52)	17 (0.81)	42 (2.00)	103 (4.90)
Observation group (n = 985)	5 (0.51)	1 (0.10)	9 (0.91)	20 (2.03)
Low-lying placenta subgroup (n = 185)	2 (1.08)	1 (0.54)	2 (1.08)	7 (3.78)
Placenta previa subgroup (n = 800)	3 (0.38)	0 (0.00)	7 (0.88)	13 (1.63)

Table 3. Logistic regression analysis on the influencing factors of hypertensive disorders of pregnancy in all patients.

Variables	Groups	B	SE	Wald	p	OR	95% CI
Age (years)		0.050	0.018	7.768	0.005	1.051	1.015, 1.089
Gestational age (weeks)		-0.340	0.025	186.092	<0.001	0.712	0.678, 0.748
Gravidity		-0.127	0.080	2.540	0.111	0.881	0.754, 1.030
Parity		-0.084	0.169	0.249	0.618	0.919	0.660, 1.280
Abnormal placental location	No*/Yes	-1.380	0.269	26.348	<0.001	0.252	0.149, 0.426
PAS	No*/Yes	-0.423	0.324	1.704	0.192	0.655	0.347, 1.236
GDM	No*/Yes	0.475	0.179	7.019	0.008	1.608	1.132, 2.286

Note: * indicated control group. PAS, placenta accreta spectrum; GDM, gestational diabetes mellitus; OR, odds ratio; 95% CI, 95% confidence interval.

ated with the reduction of gestational age at delivery (OR (95% CI) = 0.723 (0.686, 0.761), $p < 0.001$) and abnormal placental location (OR (95% CI) = 0.294 (0.169, 0.511), $p < 0.001$), and the increase of the GDM incidence (OR (95% CI) = 1.564 (1.070, 2.287), $p = 0.021$) (Table 4). These data confirmed that, suggesting that abnormal placental location was a protective factor of PIH.

3.3 The Association between PAS and HDPs

To further investigate the association between PAS and HDPs, the observation group was further divided into the PAS and non-PAS subgroups. The baseline characteristics of patients in the PAS and non-PAS subgroup are shown in Table 5. The HDPs occurred in 5.22% (18/345) of the patients in the non-PAS subgroup and in 2.66% (17/640) of the patients in the PAS subgroup. There was significant difference in the incidence of HDPs between the PAS and non-PAS subgroups ($\chi^2 = 4.29$, $p = 0.038$). The results of logistic regression analysis showed that the incidence of HDPs in patients with abnormal placental location was not correlated with PAS disorder (OR (95% CI) = 0.551 (0.242, 1.254), $p = 0.156$), but negatively associated with gestational age at delivery (OR (95% CI) = 0.769 (0.672, 0.880), $p < 0.001$) (Table 6), suggesting that gestational age at delivery might be an important confounding factor affecting the incidence of HDPs.

4. Discussion

The present study revealed that compared with patients with normal placental location (8.23%), the incidence of HDPs in patients with abnormal placental location (3.55%) was significantly decreased, especially in those with placenta previa. By including confounding factors (maternal age, gestational age, gravidity, parity, PAS disorders, and GDM), the incidence of HDPs or PIH was negatively correlated with abnormal placental location, suggesting that abnormal placental location was a protective factor of HDPs, especially PIH. Further subgroup analysis revealed that the PAS disorder was not an independent factor of the incidence of HDPs. These data merit further discussion.

Increasing studies have focused on the association between abnormal placental location especially placenta previa and the risk of HDPs. Our results revealed that the incidence of HDPs or PIH was negatively correlated with abnormal placental location. The following explanations may be used to interpret this finding. Firstly, the placenta implanted in the lower uterine segment of patients with may get a greater blood supply and oxygenation relative to those in the upper uterine segment, which may improve the situation of placental ischaemia and facilitate to the prevention of PIH [20,21]. Secondly, the trophoblasts attached in the lower uterine segment in placenta previa could infiltrate the helicine arteries more easily, and the deep infiltration of trophoblasts in placenta previa may also improve the blood supply and oxygenation of the placenta [22]. Although a

previous study has found a positive association between placenta previa and the risk of PIH [23], the discrepancy may be caused by many factors, such as size of subjects and different population properties. In addition, pregnancy is a dynamic development process, the basic physical condition of pregnant women, such as maternal age, gestational age, and pre-pregnancy BMI as well as the influence of other related factors during pregnancy may be associated with the occurrence of HDPs [24–27]. In our study, the confounding factors including maternal age, gestational age, gravidity, parity, PAS disorders, and GDM were included in the logistic regression analysis, excluding the effects of these clinical factors. Considering the lower incidence of HDPs in patients with abnormal placental location than those with normal placental location, we conducted that abnormal placental location was a protective factor for HDPs or PIH. Further studies are still required to confirm the inverse association between HDPs with abnormal placental location.

Furthermore, placenta previa and PAS disorder often occur together, and risk of PAS disorder was high in women with a history of Cesarean section and presenting with abnormal placental location (a low-lying placenta or placenta previa) [28]. It is reported that spiral artery remodeling is reduced in PAS disorders [29,30]. Incomplete transformation of the spiral arteries and lesions related to maternal vascular malperfusion are commonly observed in placenta-related disorders of pregnancy, such as preeclampsia [31], hinting that PAS placentation in a pregnancy complicated by placenta previa may exert greater impact on placental development and function. In addition, trophoblasts will infiltrate more deeply in placenta previa when concurrent placenta accreta occurs [32,33]. Compared to in women with preeclampsia, the expression of cytokines that promote the infiltration of trophoblasts like kallikrein and endothelial nitric oxide synthase is remarkably increased in women with placenta previa [34]. These data suggest that the trend toward a reduction in the incidence of HDPs might be more significant when concurrent placenta previa and PAS disorder occurs. Unfortunately, our results revealed that the incidence of HDPs was not associated with PAS disorder. This result implies that multiple factors are involved in HDPs, and decreased infiltration of trophoblasts and superficial implantation of the placenta caused by its incomplete vascular remodeling and reduced infiltration of trophoblasts are just two possible factors [35]. Whether there is the correlation between HDPs and PAS disorder requires further investigation.

The strength of this study is the large sample size of patients with normal and abnormal placental locations being compared. However, the retrospective design is the weakness of this study. Moreover, it is known that patients with known placenta previa, low-lying placenta, or PAS will always have earlier planned deliveries than patients with normal placentation. Although gestational age was controlled for in the logistic regression, it could not

Table 4. Logistic regression analysis on the influencing factors of pregnancy-induced hypertension (PIH).

Variables	Groups	B	SE	Wald	<i>p</i>	OR	95% CI
Age (years)		0.029	0.020	2.255	0.133	1.030	0.991, 1.070
Gestational age (weeks)		−0.325	0.026	153.330	0.000	0.723	0.686, 0.761
Gravidity		−0.089	0.085	1.094	0.296	0.915	0.775, 1.080
Parity		−0.147	0.183	0.648	0.421	0.863	0.603, 1.235
Abnormal placental location	No*/Yes	−1.224	0.282	18.829	<0.001	0.294	0.169, 0.511
PAS	No*/Yes	−0.675	0.360	3.507	0.061	0.509	0.251, 1.032
GDM	No*/Yes	0.447	0.194	5.325	0.021	1.564	1.070, 2.287

Note: * indicated control group. PAS, placenta accreta spectrum; GDM, gestational diabetes mellitus; OR, odds ratio; 95% CI, 95% confidence interval.

Table 5. Baseline characteristics of patients in the PAS and non-PAS subgroups.

Groups/Characteristics	Age (years)	Gestational age (weeks)	BMI	Gravidity (%)					Parity (%)				GDM (%)
	[Mean ± SD]	[Median (p25, p75)]	[Mean ± SD]	G1	G2	G3	G4	≥G5	P1	P2	P3	P4	
No-PAS subgroup (n = 345)	32.48 ± 4.92	36 (35, 37)	27.43 ± 3.39	54 (15.65)	95 (27.54)	77 (22.32)	72 (20.87)	47 (13.62)	102 (29.57)	210 (60.87)	32 (9.28)	1 (0.29)	58 (16.81)
PAS subgroup (n = 640)	33.12 ± 4.73	36 (35, 37)	28.12 ± 3.56	17 (2.66)	130 (20.31)	189 (29.53)	147 (22.97)	157 (24.53)	43 (6.72)	437 (68.28)	151 (23.59)	9 (1.41)	85 (13.28)
<i>t/Z/χ²</i>	−1.991	−4.850	−2.774	−6.582	−9.739								2.251
<i>p</i> value	0.047	<0.001	0.006	<0.001	<0.001								0.134

BMI, body mass index; PAS, placenta accreta spectrum; GDM, gestational diabetes mellitus.

Table 6. Logistic regression analysis on the influencing factors of hypertensive disorders of pregnancy in patients with abnormal placental attachment location.

Variables	Groups	B	SE	Wald	<i>p</i>	OR	95% CI
Age (years)		0.039	0.040	0.938	0.333	1.040	0.961, 1.125
Gestational age (weeks)		−0.263	0.069	14.589	<0.001	0.769	0.672, 0.880
Gravidity		−0.099	0.163	0.371	0.542	0.906	0.658, 1.246
Parity		−0.307	0.402	0.583	0.445	0.736	0.335, 1.618
PAS	No*/Yes	−0.595	0.419	2.016	0.156	0.551	0.242, 1.254
GDM	No*/Yes	0.713	0.466	2.343	0.126	2.040	0.819, 5.080
Abnormal placental location	No*/Yes	−0.532	0.443	1.442	0.230	0.588	0.247, 1.400

Note: * indicated non-PAS group. BMI, body mass index; PAS, placenta accreta spectrum; GDM, gestational diabetes mellitus; OR, odds ratio; 95% CI, 95% confidence interval.

account for patients who might have gone on to develop term preeclampsia but had a medically-indicated delivery due to placental reasons. Furthermore, there are no biochemical markers available which have been shown to identify patients at higher risk for developing preeclampsia within the next week. Further well-designed studies are warrant to confirm our findings.

5. Conclusions

Our findings reveal that there is a decreased incidence of HDPs in pregnancies with abnormal placental location and PAS disorder. Abnormal placental location is a protective factor for HDPs, especially PIH, but PAS disorder is not.

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by HL and XW. The first draft of the manuscript was written by HL and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of Shandong Provincial Hospital (SWYX: NO.2021-353).

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Conflict of Interest

The authors declare no conflict of interest.

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