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Research on the Polymorphism of Folate Metabolism Genes and Its Correlation with Pregnancy-Induced Hypertension in Women of Childbearing Age in the Neijiang Region

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Abstract: *Objective*: To explore the polymorphism of folate metabolism genes and its correlation with pregnancy-induced hypertension (PIH) in women of childbearing age in the Neijiang region. *Methods*: Forty-five pregnant women with hypertension disorders who received prenatal care at the Maternal and Child Health Hospital in the Neijiang region from May 2023 to April 2025 were selected for the study and designated as the case group. Additionally, 45 healthy pregnant women during the same period were selected as the control group. Venous blood samples were collected from both groups for folate metabolism gene testing, and the correlation with PIH was analyzed. *Results*: There were statistically significant differences in BMI index, systolic blood pressure, diastolic blood pressure, serum folate levels, Hcy levels, and vitamin B12 levels between the case group and the control group ($p < 0.05$). The proportions of MTHFR-wild type and MTRR-wild type in the case group were lower than those in the control group, while the proportions of MTHFR-heterozygous mutant type and MTRR-heterozygous mutant type were higher in the case group ($p < 0.05$). The Logistic regression model showed that overweight/obesity, abnormal folate levels, abnormal Hcy levels, abnormal vitamin B12 levels, MTHFR-heterozygous mutant type, and (repeated entry corrected to another relevant factor if necessary, but assuming it's a typo and should be another mutant type or omitted for clarity, here kept as is for direct translation) MTHFR-heterozygous mutant type (note: this repetition should likely be corrected in the original text, e.g., to MTRR-heterozygous mutant type or another relevant factor) were independent risk factors for the occurrence of HDP ($p < 0.05$), while MTHFR-wild type and MTRR-wild type were protective factors against HDP ($p < 0.05$). *Conclusion*: The polymorphism distribution of key genes involved in folate metabolism among women of childbearing age in Neijiang is significantly associated with the occurrence of Hypertensive Disorders of Pregnancy (HDP). Mutant genotypes of MTHFR and MTRR serve as independent risk factors for HDP, while the wild-type acts as a protective factor. Additionally, overweight/obesity, reduced serum folate levels, hyperhomocysteinemia, and vitamin B12 deficiency are also important risk indicators for the onset of HDP.

Keywords: Women of childbearing age; Polymorphism of folate metabolism genes; Hypertensive disorders of pregnancy (HDP); Correlation

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1. Introduction

Hypertensive Disorders of Pregnancy (HDP) represent a unique and common complication during pregnancy, with a complex pathogenesis. Current clinical research suggests that it results from the combined effects of multiple factors, including genetics, immunity, and environment. Folate, as a crucial B-vitamin, plays a vital role in its metabolic pathway for maintaining normal homocysteine (Hcy) levels, DNA synthesis, and methylation, particularly in pregnant women [1]. Impaired folate metabolism can lead to the accumulation of Hcy in the body, resulting in hyperhomocysteinemia (HHcy). Based on existing clinical studies, HHcy has been confirmed as an independent risk factor for cardiovascular diseases and is closely associated with the onset of HDP [2]. However, the efficiency of the folate metabolic pathway is regulated by a series of key enzymes, and polymorphisms in the genes encoding these enzymes may affect enzyme activity, thereby altering an individual's folate metabolic status and disease susceptibility. Currently, no international authoritative obstetrics and gynecology organization has issued explicit guidelines recommending routine folic acid metabolism gene testing for all high-risk pregnant women to prevent pregnancy-induced hypertension (PIH) [3]. Given this, more clinical studies are still needed to confirm the polymorphism of folic acid metabolism genes and their correlation with PIH, in order to provide evidence-based support for transforming this into standardized clinical screening and personalized intervention strategies.

2. Materials and methods

2.1. General information

Forty-five pregnant women with hypertension disorders during pregnancy who received prenatal care at the Maternal and Child Health Hospital in Neijiang from May 2023 to April 2024 were selected for inclusion in the study and designated as the case group. Additionally, 45 healthy pregnant women from the same period were selected as the control group. All participants in this trial provided informed consent, and the study has been approved by the ethics committee.

2.1.1. Inclusion criteria

(1) Pregnant women aged between 20 and 35 years
(2) The case group met the diagnostic criteria for HDP [4]
(3) Participation in this trial was voluntary, and informed consent forms were signed

2.1.2. Exclusion criteria

(1) Patients with thalassemia or iron-deficiency anemia
(2) Patients with uncontrolled endocrine or kidney diseases

2.2. Methods

Peripheral blood samples were collected from women in different groups using vacuum blood collection tubes. Simultaneously, 3 mL of venous blood was drawn from pregnant women, centrifuged at 3000 r/min for 10 minutes to separate the serum, and stored in a refrigerator at -20 ℃. The stored serum samples were subjected to folate metabolism gene testing. Based on the gene testing results, the folate metabolism gene polymorphisms of each woman enrolled in the trial were analyzed.

2.3. Observation indicators

When pregnant women consented to participate in the trial, their basic information, including age and education level, was collected through face-to-face interviews and questionnaires. For pregnant women enrolled in the trial, during each prenatal check-up, healthcare professionals provided advice and conducted relevant physical examinations based on the pregnant women's health status, including measurements of body mass index (BMI) and blood pressure. BMI was referenced against previous standards, with overweight pregnant women defined as those with a BMI of 24.0–27.9 kg/m^2, and obese pregnant women defined as those with a BMI ≥ 28.0 kg/m^2 [5]. The reference ranges for folate levels in pregnant women during early, middle, and late pregnancy were 3.25–85.1 ng/mL, 7.42–44.49 ng/mL, and 6.69–38.92 ng/mL, respectively. The normal range for homocysteine (Hcy) was 4.60–12.44 μmol/L, and the critical value for vitamin B12 levels was set at 150 pg/mL.

2.4. Statistical methods

Statistical analysis of the data was performed using the statistical software SPSS 19.0. The comparison of genotype distributions of gene loci between groups was conducted using the χ^2 test, while the comparison of serum markers between groups was performed using the independent samples *t*-test. Logistic regression analysis was employed to analyze the risk of gestational hypertension, with a significance level set at $p < 0.05$ indicating statistically significant differences.

3. Results

3.1. Comparison of general information between the two groups

There were statistically significant differences in BMI index, systolic blood pressure, diastolic blood pressure, serum folate levels, Hcy levels, and vitamin B12 levels between the case group and the control group ($p < 0.05$). See **Table 1**.

Table 1. Comparison of general information of pregnant women between the two groups

General characteristics	Case group (n = 45)	Control group (n = 45)	t / χ^2	p
Age (years)	26.83 ± 2.47	26.91 ± 2.51	0.152	0.789
BMI (kg/m^2)	28.76 ± 2.34	25.48 ± 2.29	6.720	< 0.001
Systolic BP (mmHg)	148.36 ± 8.47	116.82 ± 7.93	18.235	< 0.001
Diastolic BP (mmHg)	96.28 ± 6.51	75.41 ± 6.02	16.198	< 0.001
Education level (n)			0.067	0.796
High school or below	10 (22.22)	9 (20.00)		
College or above	35 (77.78)	36 (80.00)		
Serum folate (nmol/L)	15.62 ± 3.38	36.24 ± 3.67	27.724	< 0.001
Hcy (μmol/L)	14.28 ± 2.74	8.47 ± 1.69	12.107	< 0.001
Vitamin B12 (pg/mL)	305.73 ± 46.82	341.86 ± 49.31	3.564	0.001

3.2. Comparison of folate metabolism gene polymorphism distribution between the two groups

The proportions of MTHFR-wild type and MTRR-wild type in the case group were lower than those in the control group, while the proportions of MTHFR-heterozygous mutant type and MTRR-heterozygous mutant type were higher in the case group than in the control group ($p < 0.05$). See **Table 2** and **3**.

Table 2. Comparison of folate metabolism gene MTHFR polymorphism distribution between the two groups [n(%)]

Group	n	Wild type	Heterozygous mutation	Homozygous mutation
Case group	45	20 (44.44)	20 (44.44)	5 (11.11)
Control group	45	36 (80.00)	9 (20.00)	0 (0.00)
χ^2		12.101	6.156	-
p		0.001	0.013	0.056

Note: "-" indicates Fisher's exact test.

Table 3. Comparison of folate metabolism gene MTRR polymorphism distribution between the two groups [n(%)]

Group	n	Wild type	Heterozygous mutation	Homozygous mutation
Case group	45	15 (33.33)	25 (55.56)	5 (11.11)
Control group	45	27 (60.00)	15 (33.33)	3 (6.67)
χ^2		6.429	4.500	0.137
p		0.011	0.034	0.711

3.3. Correlation between research indicators and HDP based on logistic regression analysis

The statistically significant indicators from **Table 1**, **Table 2**, and **Table 3** were incorporated into a binary logistic regression model for analysis. The results indicated that overweight/obesity, abnormal folate levels, abnormal Hcy levels, abnormal vitamin B12 levels, MTHFR-heterozygous mutation, and MTHFR-homozygous mutation were independent risk factors for the occurrence of HDP ($p < 0.05$). Conversely, MTHFR-wild type and MTRR-wild type were protective factors against HDP ($p < 0.05$). See **Table 4**.

Table 4. Binary logistic regression model analysis of factors influencing the occurrence of HDP

Influencing factor	β	SE	p	OR	95% CI
Overweight / Obesity	1.288	0.444	0.004	3.625	1.519–8.651
Abnormal folate	1.520	0.478	0.001	4.571	1.792–11.660
Abnormal Hcy	1.476	0.467	0.002	4.375	1.750–10.938
Abnormal Vitamin B12	1.342	0.477	0.005	3.826	1.501–9.752
MTHFR - Wild Type	-1.609	0.480	0.001	0.200	0.078–0.514
MTHFR - Heterozygous mutation	1.163	0.478	0.015	3.200	1.253–8.172
MTRR - Wild type	-1.100	0.438	0.012	0.333	0.141–0.786
MTRR - Heterozygous mutation	0.916	0.436	0.036	2.500	1.064–5.874

4. Discussion

HDP is one of the leading causes of morbidity and mortality among pregnant women and perinatal infants worldwide. In recent years, with the advancement of precision medicine, gene polymorphisms in the folate metabolic pathway have been recognized as significant genetic susceptibility factors for HDP [6]. Folate metabolism plays a crucial role in cell proliferation, DNA synthesis and repair, and the regulation of DNA methylation. Methylenetetrahydrofolate reductase (MTHFR) and methionine synthase reductase (MTRR), as key enzymes in this pathway, may have their activities affected by gene polymorphisms, thereby altering metabolite levels and increasing the risk of HDP.

In this study, it was observed that the proportions of MTHFR-wild type and MTRR-wild type in the case group were lower than those in the control group, while the proportions of MTHFR-heterozygous mutant type and MTRR-heterozygous mutant type were higher than those in the control group ($p < 0.05$). The reason for this lies in the fact that although the homozygous mutant type carries the highest risk, its absolute frequency in the population is far lower than that of the heterozygous type. Although the individual risk of the heterozygous type is lower than that of the homozygous mutant type, its absolute number may be the largest due to its large population base. Additionally, studies have shown that individuals carrying the MTHFR C677T heterozygous mutation have MTHFR enzyme activity approximately 65% to 70% of that of the wild type, and the MTRR A66G heterozygous mutation also leads to partial impairment of enzyme function [7]. Reduced enzyme activity results in decreased production of 5-methyltetrahydrofolate, which in turn elevates plasma homocysteine (Hcy) levels. Elevated Hcy can induce endothelial dysfunction, oxidative stress, vascular inflammation, and a propensity for thrombosis, potentially exacerbating placental vascular endothelial damage and blood pressure regulation imbalance during pregnancy, thereby increasing the risk of hypertension. Furthermore, homocysteine accumulation may also activate the renin-angiotensin system, further exacerbating vasoconstriction and renal damage [8].

Therefore, in this study, abnormal Hcy levels, MTHFR-heterozygous mutant type, and MTRR-heterozygous mutant type were identified as independent risk factors for the occurrence of hypertensive disorders of pregnancy (HDP). This study also observed that overweight/obesity, abnormal folate levels, and abnormal vitamin B12 levels are similarly risk factors for hypertensive disorders of pregnancy (HDP). Overweight/obesity can lead to adverse placental perfusion and oxidative damage to placental tissue, resulting in maternal arterial dysfunction and blood flow disorders, thereby increasing the risk of HDP. Furthermore, the inflammatory response, endothelial dysfunction, and oxidative stress caused by obesity itself can also exacerbate the risk of HDP [9]. Abnormal folate and vitamin B12 levels exacerbate homocysteine (Hcy) accumulation through one-carbon metabolism disorders, inducing oxidative stress and vascular dysfunction. Previous studies have similarly confirmed these factors as risk factors that exacerbate the risk of HDP, consistent with the findings of this study [10]. However, as a single-center study with a small sample size, this research is subject to selection bias, and thus the generalizability of its results remains to be validated through further multi-center, large-sample studies. Additionally, it must be noted that folate metabolism is also influenced by various factors such as dietary intake and supplement use. Although this study controlled for some confounding factors, it did not comprehensively collect and analyze all possible interfering information, which may have had an impact on the final results.

5. Conclusion

In summary, this study found that among women of childbearing age in the Neijiang region, MTHFR C677T and MTRR A66G gene polymorphisms are closely associated with the risk of developing hypertensive disorders

of pregnancy. Pregnant women carrying mutant genotypes, who concurrently exhibit abnormalities in folate metabolism-related indicators (low folate, high homocysteine (Hcy), and low vitamin B12) and are overweight/obese, face a significantly increased risk of developing hypertensive disorders of pregnancy (HDP). Therefore, for pregnant women with the aforementioned high-risk factors, conducting polymorphic screening of key genes in the folate metabolic pathway and performing risk assessments based on their metabolic status hold potential clinical value in formulating personalized folate intervention strategies and achieving early prevention of HDP.

Disclosure statement

The author declares no conflict of interest.

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