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Effect of serum high molecular weight adiponectin level on the occurrence of eclampsia during subsequent pregnancy in patients with primary pregnancy induced hypertension

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Abstract. – OBJECTIVE: To analyze the effect of serum levels of high molecular weight adiponectin (HMWA) on the occurrence of eclampsia during subsequent pregnancy in patients with primary pregnancy-induced hypertension (PIH).

PATIENTS AND METHODS: Thirty patients with primary PIH (observation group) and sixty patients without primary PIH (control group) were consecutively selected. ELISA was used to measure the serum levels of HMWA. The differences in the occurrence of eclampsia during subsequent pregnancy between the two groups were compared.

RESULTS: The serum levels of HMWA in the observation group were significantly lower than in the control group, and they decreased with increased severity of PIH ($p < 0.05$). In the observation group, the gestational age was lower than that of the control group, and the occurrence of cesarean section and maternal complications were increased. The neonatal weight and Apgar scores were lower than those of the control group, and the occurrence of neonatal complications was increased. The difference was statistically significant ($p < 0.05$). There were no differences in the time intervals between pregnancies in the two groups. The occurrence of PIH and eclampsia during subsequent pregnancy in the observation group was significantly higher than that in the control group ($p < 0.05$). According to receiver operating curve analysis, the sensitivity, specificity, and accuracy of serum HMWA level in predicting the occurrence of eclampsia during subsequent pregnancy were 85.6%, 74.8%, and 0.824 (95% CI = 0.811-0.936, $p = 0.015$), respectively. The critical value was 2.4 mg/l.

CONCLUSIONS: Decreases of serum levels of HMWA in patients with primary PIH are closely related to the severity of PIH and the outcome of pregnancy, which has important predictive value for the occurrence of eclampsia during subsequent pregnancy.

Key Words:
Pregnancy induced hypertension, High molecular weight adiponectin, Eclampsia, Receiver operating curve.

Introduction

Pregnancy-induced hypertension (PIH) includes hypertensive disorders that complicate pregnancy, such as preeclampsia, eclampsia, preeclampsia combined chronic hypertension, and chronic hypertension[1]. It is a leading cause of maternal and perinatal complications and death, with a morbidity rate of roughly 7-15%[2]. Shallow placental implantation, ischemic anoxia of trophoblasts, vascular endothelial cell injury, immune and inflammatory reaction disorders, thrombosis, and other mechanisms play important roles in the occurrence of PIH[3]. Adiponectin is an endogenous hormone polypeptide secreted by adipocytes, with an active form that is a polymer complex. It plays an important role in regulating fatty acid oxidation, sugar metabolism, and endothelial function[4]. Studies[5] confirmed that adiponectin is a protective factor of the cardiovascular system with antihypertensive effects, an insulin sensitization factor, and it

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reduces the risk of insulin resistance and type 2 diabetes mellitus[6]. Studies[7] have shown that reduction of serum high molecular weight adiponectin (HMWA) correlates with the severity of PIH and can predict the disease outcome. The objective of the present study was to further analyze the effect of serum levels of HMWA in patients with primary PIH on eclampsia in the subsequent pregnancy.

Patients and Methods

Patients

Thirty patients diagnosed with PIH admitted to our hospital between January 2013 and January 2016 were consecutively selected as the observation group. Sixty patients without PIH were selected as the control group. The inclusion criteria included: (1) Patients who were in their first pregnancy had no history of induced abortion, and gestational age ≥ 20 weeks; (2) Patients with single-birth pregnancies, and with no malposition of the fetus; (3) Patients with complete medical history. The exclusion criteria included: (1) Patients with other gestational diseases such as cardiovascular disease, diabetes mellitus, autoimmune diseases, and hematologic diseases; (2) Patients who required a cesarean section. The age of patients in the observation group ranged from 22-45 years old, and the median age was 26.7 years old. The gestational age ranged from 25-33 weeks, and the average was 28.5 ± 3.6 weeks. Body mass index (BMI) ranged from 23.2-26.8 kg/m^2, with average of 24.5 ± 2.7 kg/m^2. There were 18 cases of mild PIH, nine cases of moderate PIH, and three cases of severe PIH (including preeclampsia and eclampsia). The age of patients in the control group ranged from 21-44 years old, and the median age was 26.5 years old. The gestational age ranged from 23-32 weeks, with an average of 27.6 ± 4.4 weeks. BMI was 23.3-27.2 kg/m^2, with an average of 24.8 ± 2.9 kg/m^2. The baseline parameters of patients in the two groups were comparable. This study was approved by the Ethics Committee of the first Affiliated Hospital of Zhengzhou University. Signed written informed consents were obtained from all participants before the study.

Research Methods

All patients were pregnant twice. ELISA was used to measure the levels of serum HMWA. The kit was from Jiangsu Biyuntian Technology (Co. Ltd. Jiangsu, China). The outcomes of the first pregnancy, including the gestational age, mode of pregnancy, maternal complications, neonatal weight, Apgar score, neonatal complications, time interval between pregnancies, and the occurrence of PIH and eclampsia during the second pregnancy were compared.

Statistical Analysis

Data were analyzed with SPSS 20.0 (SPSS Inc., Chicago, IL, USA). Normally distributed data are presented as a mean ± standard deviation and were compared with a *t*-test. Qualitative data are presented as rate and were compared with a χ^2-test. The sensitivity and specificity of the levels of serum HMWA for predicting the occurrence of eclampsia during the subsequent pregnancy were analyzed by receiver operating curves (ROC). The accuracy was presented by the area under the curve (AUC). Statistical significance was defined as $p < 0.05$.

Results

Comparison of Levels of Serum HMWA

The serum levels of HMWA in the observation group were significantly lower than in the control group, and they decreased with increased severity of PIH ($p < 0.05$) (Figure 1).

Comparison of the Gestational Age of the first Pregnancy, Mode of Pregnancy, and Maternal Complications

The gestational age of the observation group was lower than that of the control group, and the occurrences of cesarean section and complications were increased. The differences were statistically significant ($p < 0.05$) (Table I).

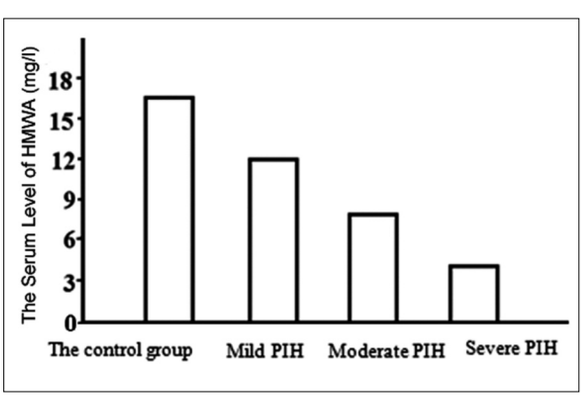

Figure 1. Comparison of serum HMWA level. HMWA: high molecular weight adiponectin.

Table I. Comparison of the gestational week of the first pregnancy, mode of pregnancy, and maternal complications.

Group	Cases	The gestational age (weeks)	Eutocia	Cesarean section	Hemorrhage (> 1000 ml)	Infection	Ablation placentae	Liver and kidney dysfunction	Prevalence of complications
The control group	60	39.5 ±1.8	55 (91.7)	5 (8.3)	0	1	1	0	2 (3.3)
The observation group	30	37.6 ±2.2	21 (70.0)	9 (30.0)	2	1	2	1	6 (20.0)
t/χ^2		5.624	5.593					4.956	
p		0.018	0.018					0.026	

Table II. Comparison of neonatal weight, Apgar score, and neonatal complications.

Group	Cases	Neonatal weight (kg)	Apgar score	Hypoxic ischemic encephalopathy	Asphyxia	Death	Prevalence of complications
The control group	60	3.6 ± 0.5	8.5 ± 1.7	1	1	0	2 (3.3)
The observation group	30	3.1 ±0.9	6.3 ± 1.6	3	3	1	7 (23.3)
t/χ^2		5.432	6.235				6.806
p		0.021	0.007				0.009

Comparison of Neonatal Weight, Apgar Score, and Neonatal Complications

The neonatal weight and Apgar scores of the observation group were lower than those of the control group, and the occurrence of neonatal complications was increased. The differences were statistically significant ($p < 0.05$) (Table II).

Comparison of the Time Interval Between Pregnancies and the Occurrence of Pregnancy-induced Hypertension and Eclampsia During the Subsequent Pregnancy

There were no differences in the time intervals between pregnancies in the two groups. The occurrence of PIH and eclampsia during the subsequent pregnancy in the observation group was significantly higher than in the control group ($p <$ 0.05) (Table III).

ROC Analysis of Levels of Serum HMWA for Predicting the Occurrence of Eclampsia During the Subsequent Pregnancy

According to the ROC analysis with the serum levels of HMWA as the detection index and the occurrence of eclampsia during subsequent pregnancy as the diagnostic result, the sensitivity was 85.6%, the specificity was 74.8%, and the accuracy was 0.824. The 95% CI = 0.811-0.936, p = 0.015. The critical value was 2.4 mg/l (Figure 2).

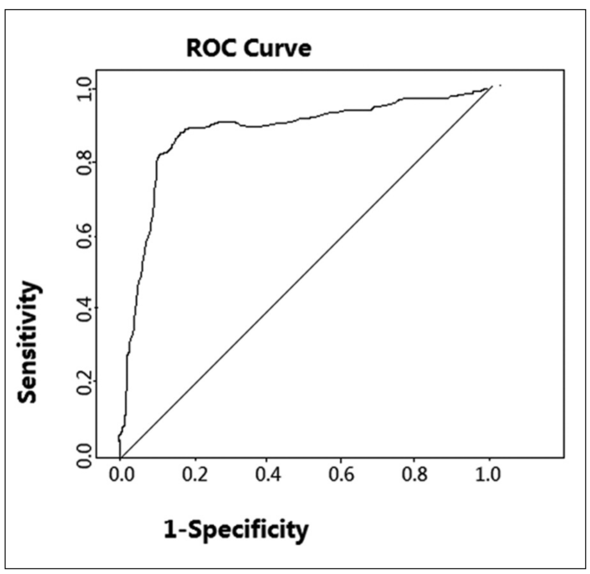

Figure 2. The ROC analysis of serum HMWA level in predicting the occurrence of eclampsia during subsequent pregnancy. ROC: receiver operating characteristic; HMWA: high molecular weight adiponectin.

Table III. Comparison of the time interval between pregnancies and the prevalence of pregnancy induced hypertension and eclampsia during the subsequent pregnancy.

Group	Cases	The time interval between the pregnancies (months)	Pregnancy induced hypertension [cases (%)]	Eclampsia [cases (%)]
The control group	60	32.5±5.6	4 (6.7)	1 (1.7)
The observation group	30	33.4±6.3	25 (83.3)	5 (16.7)
t/χ^2	0.234	53.827	5.022	
p	0.825	0.000	0.025	

Discussion

The basic pathological changes of PIH and eclampsia involve extensive vascular endothelial cell injury, vascular spasms, decreased glomerular filtration, and increased vascular permeability, resulting in persistent hypertension and proteinuria[8,10]. Adiponectin has two receptors, R1 and R2. R1 is mainly expressed in skeletal muscle, while the expression of R2 is mostly in the liver[11]. The metabolism of blood lipids and glucose is promoted by activation of the adenosine monophosphate kinase (AMPK) signaling pathway[12]. The physiological role of adiponectin is mainly to regulate glucose and lipid metabolism and to increase insulin sensitivity. It also has anti-inflammatory and anti-atherosclerotic functions. As an anti-inflammatory factory, adiponectin can reduce the production of C-reactive protein in the early stage of inflammation, activate PI3K signaling to induce nitric oxide (NO) release from vascular endothelial cells and increase the activity of endothelial NO synthase[13]. It can also inhibit the degree of inflammation of the vascular wall, protect vascular endothelium, and enhance diastolic vascular function, thereby regulating the stability of blood pressure[14]. A previous study[15] found that adiponectin could stimulate the production of the anti-inflammatory factor, IL-10, inhibit the production of the pro-inflammatory factor, IFN-γ, and reduce the levels of IL-6 and TNF-α resulting from LPS stimulation. The anti-inflammatory effects of adiponectin are mediated primarily through inhibition of NF-κB and the ERK1/2 MAPK signaling pathway[16].

Adiponectin can also inhibit the expression of serum intercellular adhesion molecule-1 (ICAM-1), E-selectin, and vascular endothelial cell adhesion molecule-1 (VCAM-1), and reduce the levels of phosphorylated IκB, resulting in the inhibition of monocyte adhesion to endothelial cells and decrease in the expression of type I scavenger receptor of macrophages. Therefore, the uptake of oxidized low-density lipoprotein (ox-LDL) by macrophages was shown to be inhibited, and the formation of foam cells was significantly reduced[17,18]. Adiponectin has an anti-inflammatory role in placental tissue and is involved in the occurrence of PIH and eclampsia[19].

Saarela et al[20] confirmed that single nucleotide polymorphisms of the adiponectin gene are related to the occurrence of preeclampsia. Preeclampsia was shown to occur with insulin resistance and high BMI, and the levels of plasma adiponectin were higher than in normal pregnancy after the correction of hematocrit[21]. However, Eleuterio et al[22], which found that the serum levels of HMWA in the observation group were significantly lower than those of the control group, and they decreased with the increase of PIH severity. At present, there is no unified understanding of the relationship between serum adiponectin levels and the occurrence of PIH. Demir et al[23] suggested that high levels of adiponectin are an independent risk factor for PIH, especially in preeclampsia. The results of this study suggested that low levels of HMWA are closely related to the occurrence and severity of PIH. In the observation group, the gestational age was lower than that of the control group, and the occurrence of cesarean section and complications was increased. The neonatal weight and Apgar scores were lower than those of the control group, and the occurrence of complications was increased. There are several factors affecting the outcome of PIH, and it may be related to serum levels of HMWA. There were no differences in the time intervals between pregnancies in the two groups. The occurrence of PIH and eclampsia

during subsequent pregnancy in the observation group was significantly higher than in the control group. According to the ROC analysis, the sensitivity, specificity, and accuracy of serum HMWA level for predicting the occurrence of eclampsia during the subsequent pregnancy were 85.6%, 74.8%, and 0.824, respectively. The critical value was 2.4 mg/l. Decreased levels of serum HMWA are closely related to the severity of PIH and the outcome of pregnancy, which has important predictive value for the occurrence of eclampsia during subsequent pregnancy.

An important aspect of this research was the analysis of the clinical outcomes of patients with PIH in two consecutive pregnancies. The levels of HMWA are stable in the body. They are not easily affected by diet, metabolism, or activity, and the variability is small. ROC analysis was used to establish reference data for the sensitivity and accuracy of HMWA in predicting the occurrence of eclampsia in a subsequent pregnancy and to identify the corresponding critical value. This type of analysis should make the clinical diagnosis and early intervention easier. A limitation of the study was that the sample size was small, and the observational indexes were limited with many bias factors.

Conclusions

Decreases of serum levels of HMWA in patients with primary PIH are closely related to the severity of PIH and the outcome of pregnancy, which has important predictive value for the occurrence of eclampsia during subsequent pregnancy.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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