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The clinical value of combined detection of N-terminal pro-brain natriuretic peptide, blood lipid, coagulation and fibrinolytic function in pregnancy induced hypertension.

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Abstract

Objective: Our objective is to explore the clinical value of combined detection of N-Terminal pro-Brain Natriuretic Peptide (NT-proBNP), blood lipid, coagulation, and fibrinolytic function in Pregnancy Induced Hypertension (PIH).

Methods: 172 PIH patients admitted in our hospital during February, 2014-August, 2016 were included in the observation group, which were divided into mild (n=81), moderate (n=52) and severe (n=39) groups according to PIH severity. Meanwhile, 140 healthy pregnant women were included in the control group. NT-proBNP, blood lipid, coagulation, and fibrinolytic function in both groups were detected and the differences were compared. The correlation analysis was used to analyze the correlation of the above indexes with Mean Arterial Pressure (MAP).

Results: The MAP, NT-proBNP, TC, HDL-C, LDL-C, FIB, D-D and FDP in the observation group were higher than those in the control group, and the PT, APTT and TT of the observation group were lower than those of the control group, the differences were statistically significant (P<0.05). With the aggravation of PIH, the MAP, NT-proBNP, TG, HDL-C, TC, LDL-C, FIB, D-D and FDP were gradually increased, and the PT, APTT and TT were gradually decreased, the differences were statistically significant (P<0.05). Pearson correlation analysis showed that NT-proBNP, TC, TG, FIBG, D-D and FDP were positively correlated with MAP in PIH and PT, APTT and TT were negatively correlated with MAP in pregnant women with PIH (P<0.05).

Conclusion: The combined detection of NT-proBNP, blood lipid, blood coagulation and fibrinolytic function can reflect the severity of PIH patients, and provide a reference for the early diagnosis, treatment and prognosis evaluation of PIH.

Keywords: N-terminal pro-brain natriuretic peptide (NT-proBNP), Blood lipid, Coagulation and fibrinolysis, Pregnancy induced hypertension syndrome (PIH).

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Introduction

Pregnancy Induced Hypertension (PIH) is a specific obstetric disease of pregnant women. It usually appears after 20 weeks of pregnancy, which is the common reason of poor prognosis or even death of perinatal infants [1-3]. In the developed countries, the morbidity of PIH is 6%-8%, and in China it's even up to 9.4% [4-6]. Thus, how to diagnose and evaluate the severity of PIH is always the key point of clinical research, which is also the key to direct the proper intervention and guarantee the outcome of mothers and infants. The previous studies have shown that in the development of PIH, N-terminal pro-brain natriuretic peptide (NT-proBNP), blood lipid, coagulation and fibrinolytic function play important roles [1,7-11]. However, there is no study related to the exploration of the comprehensive influence of the above indexes. In this study, 172 PIH patients and 140 healthy pregnant women were selected, and the correlation of the above indexes and the PIH severity were analyzed.

Materials and Methods

General data

172 PIH patients admitted in our hospital during February, 2014-August, 2016 were included in the observation group, which were divided into mild (n=81), moderate (n=52) and severe (n=39) groups according to PIH criteria. Meanwhile, 140 healthy pregnant women were included in the control group. In the observation group, the age was 22-37 y old and the average age was 26.29 ± 5.32 y old, the body weight was 46-72 kg and the average weight was 54.26 ± 9.11 kg, the gestational week was 20-37 and the average gestational week

was 27.66 ± 5.82. In the observation group, the age was 21-39 y old and the average age was 27.11 ± 5.58 y old, the body weight was 43-75 kg and the average body weight was 53.59 ± 10.63 kg, the gestational week was 20-38 and the average gestational weeks was 27.51 ± 5.90. The age, body weight, and gestational week between two groups were not statistically different (P>0.05), which were comparable. This study was approved by the Ethics Committee in our hospital, the pregnant women and the surrogates all signed the informed consent.

Inclusion criteria and exclusion criteria

The inclusion data of the observation group: the patients were conformed to the diagnostic criteria of PIH and the PIH degree was confirmed [6,12]. The inclusion data of control group: the patients received comprehensive physical examination, laboratory examination and image logical examination to confirm that they were in a good condition. Exclusion data: the patients had drug history that affects NT-proBNP, blood lipid, coagulation, or fibrinolytic function; the patients were complicated with the diseases that affect NT-proBNP, blood lipid, coagulation, or fibrinolytic function; the patients were complicated with thyroid dysfunction, heart, liver or kidney dysfunction, eclampsia, placental abruption, severe infection or malignant tumor; the patients were complicated with primary hypertension.

Detection methods

The detection of serum and plasmic indexes: 4 ml fasting venous blood on the second day was collected and kept in EDTA anti-coagulative tube. Then the tube was centrifuged at 3000 r/min for 10 min (the centrifugal radius was 13.5 cm). The serum was separated for NT-proBNP and blood lipid detection, and the plasma was separated for coagulation and fibrinolysis detection. Roche Diagnostics Elecsys 2010 Immunoassay Analyzer (F. Hoffmann-La Roche Ltd., Basel, Switzerland) was used to detect NT-proBNP by electro-chemiluminescence immunoassay, the kit was purchased from F. Hoffmann-La Roche Ltd., Basel, Switzerland; Hitachi 7180 Automatic Biochemical Analyzer (Hitachi, Ltd., Tokyo, Japan) was used to detect blood lipid indexes, including Total Cholesterol (TC), Triacylglycerol (TG), High Density Lipoprotein Cholesterol (HDL-C) and Low Density Lipoprotein Cholesterol (LDL-C); Sysmex CS-5100 Automated Coagulation Analyzer (Simens Co., Munich, Germany) was used to detect coagulation and fibrinolytic function by coagulation method and immunoturbidimetry, including Prothrombin time (PT), Activated Partial Thromboplastin Time (APTT), Thrombin Time (TT), Fibrinogen (FIB), D-Dimer (D-D) and Fibrin Degradation Product (FDP), all the kits were purchased from Simens Co., Munich, Germany.

Detection of Mean Arterial Pressure (MAP): 24 h dynamic blood pressure values of pregnant women were monitored by dynamic blood pressure analyzer. The blood pressure values at 6:00-8:00, 16:00-18:00 (peak time) and 2:00-3:00 (off-peak time) were recorded and MAP was calculated based on those values.

Statistical analysis

All the data in this clinical research were analyzed by SPSS 18.0 (International Business Machines Corp., New York, USA), the enumeration data were presented by (n/%) and analyzed by χ^2, and the measurement data were presented by ($\bar{x}$ ± s) and analyzed by t-test. The correlation was analyzed by Pearson correlation analysis and P<0.05 was considered as statistically significant.

Results

Comparison of indexes between the observation group and control group

The MAP, NT-proBNP, TC, HDL-C, LDL-C, FIB, D-D, FDP in the observation group were higher than those in the control group, and the PT, APTT and TT of the observation group were lower than those of the control group, the differences were statistically significant (P<0.05), as shown in Table 1.

Table 1. *Comparison of NT-proBNP, blood lipid, coagulation and fibrinolytic function and MAP between the observation and control group ($\bar{x}$ ± s).*

Index	Observation group (n=172)	Control group (n=140)	P value
MAP (kPa)	17.65 ± 1.38	11.26 ± 1.13	<0.05
NT-proBNP (pg/mL)	126.39 ± 31.54	38.85 ± 7.19	<0.05
TC (mmol/L)	5.81 ± 1.35	4.23 ± 0.87	<0.05
TG (mmol/L)	3.75 ± 1.63	1.86 ± 0.52	<0.05
HDL-C (mmol/L)	1.69 ± 0.53	1.60 ± 0.37	<0.05
LDL-C (mmol/L)	3.11 ± 0.92	2.46 ± 0.60	<0.05
PT (s)	10.31 ± 2.06	12.67 ± 1.37	<0.05
APTT (s)	23.24 ± 3.18	30.26 ± 2.85	<0.05
FIB (g/L)	5.67 ± 0.99	3.62 ± 0.85	<0.05
TT (s)	12.13 ± 2.45	17.26 ± 1.27	<0.05
D-D (mg/L)	28.29 ± 1.07	1.43 ± 0.39	<0.05
FDP (μg/L)	18.26 ± 3.58	2.97 ± 1.65	<0.05

Comparison of NT-proBNP, blood lipid, coagulation, fibrinolytic function and MAP between the pregnant women with different PIH severity

With the aggravation of PIH, the MAP, NT-proBNP, TG, HDL-C, TC, LDL-C, FIB, D-D and FDP were gradually increased, and the PT, APTT and TT were gradually decreased, and the

differences were statistically significant (P<0.05), as shown in Table 2.

Table 2. *Comparison of different indexes between the pregnant women with different PIH severity ($\bar{x} \pm s$).*

Index	Mild group (n=81)	Moderate group (n=52)	Severe group (n=39)	P value
MAP (kPa)	13.62 ± 1.38	15.69 ± 1.55*	18.86 ± 1.24*#	<0.05
NT-proBNP (pg/mL)	96.62 ± 10.82	119.26 ± 25.48*	196.39 ± 30.52*#	<0.05
TC (mmol/L)	5.71 ± 1.33	5.96 ± 1.52*	7.64 ± 2.08*#	<0.05
TG (mmol/L)	3.21 ± 0.91	3.85 ± 1.53*	4.37 ± 1.36*#	<0.05
HDL-C (mmol/L)	1.62 ± 0.48	1.69 ± 0.53*	1.92 ± 0.58*#	<0.05
LDL-C (mmol/L)	4.07 ± 0.83	4.26 ± 1.34*	5.66 ± 1.70*#	<0.05
PT (s)	11.48 ± 2.36	10.52 ± 2.11*	9.18 ± 2.06*#	<0.05
APTT (s)	25.48 ± 2.13	23.54 ± 3.04*	21.09 ± 2.25*#	<0.05
FIB (g/L)	4.82 ± 1.04	5.53 ± 0.98*	6.11 ± 0.75*#	<0.05
TT (s)	14.68 ± 2.39	12.14 ± 2.22*	11.46 ± 2.40*#	<0.05
D-D (mg/L)	15.37 ± 1.62	28.87 ± 1.15*	36.08 ± 2.41*#	<0.05
FDP (μg/L)	10.46 ± 1.49	18.33 ± 3.49*	25.26 ± 3.88*#	<0.05

Note: *P<0.05 compared with the mild group; #P<0.05 compared with the mild group.

Correlation analysis

Pearson correlation analysis showed that NT-proBNP, TC, TG, FIBG, D-D and FDP were positively correlated with MAP in PIH, and PT, APTT and TT were negatively correlated with MAP in pregnant women with PIH (P<0.05), as shown in Table 3.

Table 3. *The correlation analysis of NT-proBNP, blood lipid, coagulation and fibrinolytic function with MAP.*

Index	R value	P value
NT-proBNP	0.613	<0.05
TC	0.559	<0.05
TG	0.538	<0.05
HDL-C	0.162	>0.05
LDL-C	0.231	>0.05
PT	-0.689	<0.05
APTT	-0.542	<0.05
FIB	0.618	<0.05
TT	-0.492	<0.05
D-D	0.558	<0.05
FDP	0.628	<0.05

Discussion

During the pregnancy, the physical volume load is significantly increased, manifesting as the increase of the preload volume and left ventricle muscle mass, which is the main reason of the abnormity of hemodynamics and even the development of PIH [13-18]. As a disease that significantly affects the health of pregnant women and perinatal infants, PIH can cause the spasm of arteriole and increase of peripheral arterial resistance, and further increase the afterload of left ventricle. As the continuous development of PIH, the myocardial fiber remodelling is more and more obvious, which further causes concentric hypertrophy and left ventricle function change [19-21]. Thus, some scholars consider that due to that NT-proBNP can reflect the ventricular filling pressure increase and cardiocyte traction and the level is related to the cardiac function, serum NT-proBNP is expected to indicate the PIH severity [22].

In this study, NT-proBNP was combined with blood lipid, coagulation and fibrinolytic function to indicate the PIH severity. The results showed that except HDL-C and LDL-C, the other indexes were all related to PIH security, the mechanism may be the following: NT-proBNP is a biomarker that resists the increase of blood pressure, as the increase of the blood pressure the serum concentration is usually obviously increased to have diuretic, natriuretic and blood vessel dilating functions, and antagonize the volume load increase in PIH [23-26]. As the progress of PIH, MAP of the pregnant women is significantly increased, NT-proBNP concentration is also increased, which is considered as a sensitive index of PIH; the results also showed that as the progress of PIH, the hyperlipemia manifestation was more obvious, which is considered to be related to the decreased colloid osmotic pressure and increased urinary albumin excretion caused by PIH. These pathological changes can cause vascular endothelial injury and aggravated arteriosclerosis, and then further affect the development of the foetus [12,27-29]. In the severe cases, there is even hypoxia, organ failure and even death due to the decrease of anti-vascular disease ability; compared with the healthy pregnant women, PIH women are in coagulation and fibrinolysis unbalanced status manifesting as decreased PT, APTT, TT and increased FIB, D-D, FDP. Decreased PT indicates that some serum coagulation factors such as I, II, V, VI and X are activated, at that time the blood is at a hypercoagulation status and the thrombus formation risk is very high [30]. APTT can not only reflect the status of coagulation factor activation, but is also closely related to the prekallikrein activation, and shortened APTT is related to the endogenous blood coagulation [31]. Shortened TT indicates that the plasma heparinoids and fibrin degradation product are increased [32]. The fibrinmonomer produced from fibrin by the thrombin mainly participate in the hemostatic process. Thus, the change of TT and FIB indicate that the body of PIH women is in a prethrombotic state [33]. As the increase of severity, the risk of thrombus is increased and is more reliable to have

eclampsia. The increase of D-D and FDP indicates that the body is at a coagulation and fibrinolysis activated state, in this case there are primary and secondary hyperfibrinolysis and the coagulation factors are significantly consumed. Thus there is high risk of thrombus formation and postpartum haemorrhage, and the risk of kidney failure is also increased [34,35].

In clinical practice, the evaluation of PIH is always a difficult point, and the early prediction of PIH is also a big difficulty in medical field. In this study, NT-proBNP, blood lipid, coagulation, and fibrinolytic function were all different between the PIH and non-PIH patients, or different PIH degree. The above indexes are correlated to the MAP of pregnant women. Thus, the combined detection of the above indexes can provide a reference for the early diagnosis, disease evaluation, treatment decision and prognosis judgment, which is worthy of further attention.

The limitation of this is that the diagnostic criteria are a relatively older version, which may cause the screening omission of some patients. Besides, the sample volume in this study is only 172, which cannot fully reflect the whole PIH population in China. In the further study, a larger size prospective analysis will be conducted to further clarify the effects of the NT pro-BP, blood lipid, coagulation and fibrinolytic function on the diagnosis and treatment of PIH.

References

1. Aoyagi R, Hayashi T, Tsuneoka H. Choroidal thickening and macular serous retinal detachment in pregnancy-induced hypertension. Int Med Case Rep J 2015; 8: 291-294.
2. Kemse N, Kale A, Joshi S. Maternal supplementation of omega-3 fatty acids and micronutrients reduces cardio-metabolic variables in pregnancy induced hypertension rats. Life Sci 2016; 155: 85-93.
3. Qasim A, Bashir A, Sajid S, Riaz MM, Almas A. Women with pregnancy induced hypertension have a higher risk of developing essential hypertension-a case control study from a tertiary care center in Pakistan. J Pak Med Assoc 2016; 66: 179-183.
4. Ochi H, Kusanagi Y, Katayama T, Matsubara K, Ito M. Clinical significance of normalization of uterine artery pulsatility index with maternal heart rate for the evaluation of uterine circulation in pregnancy-induced hypertension. Ultrasound Obstet Gynecol 2003; 21: 459-463.
5. Pal GK, Shyma P, Habeebullah S, Shyjus P, Pal P. Spectral analysis of heart rate variability for early prediction of pregnancy-induced hypertension. Clin Exp Hypertens 2009; 31: 330-341.
6. Shibata T, Nakago S, Kato H, Tokuda H, Matsuki R, Kotsuji F. Management of severe pregnancy-induced hypertension after 34 weeks of gestation: A prospective study to reduce the rate of cesarean section. Hypertens Pregnancy 2016; 35: 82-90.
7. Liang X, Lin Y, Cheng Y. Changes in plasma endothelin-1 and lipid peroxidate levels and amount of superoxidate dismutase in red blood cell in patients with pregnancy-induced hypertension. Zhonghua Fu Chan Ke Za Zhi 1996; 31: 220-222.
8. Lutnicki K, Zych I, Rola R, Paszkowski T, Wrobel J. Levels of lipid peroxidation products in blood serum and placental tissue of women with pregnancy induced hypertension. Ginekol Pol 1998; 69: 895-901.
9. Patel N, Riordan-Eva P, Chong V. Persistent visual loss after retinochoroidal infarction in pregnancy-induced hypertension and disseminated intravascular coagulation. J Neuroophthalmol 2005; 25: 128-130.
10. Shi Q, Chen C, Wang XF, Wang HL. Clinical study of hemostatic coagulation markers in prethrombosis state of pregnancy induced hypertension. Zhonghua Fu Chan Ke Za Zhi 2004; 39: 733-736.
11. Mukai Y, Sato S. Effect of nitric oxide deficiency on tissue-type plasminogen activator expression in the umbilical cord in a pregnancy-induced hypertension rat model. Pregnancy Hypertens 2012; 2: 53-58.
12. Singh M, Pathak MS, Paul A. A study on atherogenic indices of pregnancy induced hypertension patients as compared to normal pregnant women. J Clin Diagn Res 2015; 9: 05-08.
13. Hasegawa J, Ikeda T, Sekizawa A, Tanaka H, Nakata M, Murakoshi T, Katsuragi S, Osato K, Ishiwata I, Kinoshita K. Maternal death due to stroke associated with pregnancy-induced hypertension. Circ J 2015; 79: 1835-1840.
14. Miao HW, Gong H. Correlation of ACE gene deletion/insertion polymorphism and risk of pregnancy-induced hypertension: a meta-analysis based on 10,236 subjects. J Renin Angiotensin Aldosterone Syst 2015; 16: 982-994.
15. Pranita Kumar A, Shahi S, Choudhary D. Posterior reversible encephelopathy syndrome presenting as quadriparesis in pregnancy induced hypertension. J Clin Diagn Res 2015; 9: 08-09.
16. Ai L, Lan X, Wang L, Xu Y, Zhang B. Clinical study on the influence of phloroglucinol on plasma angiotensin II and D-Dimer index in patients with severe pregnancy-induced hypertension. Pak J Pharm Sci 2016; 29: 1375-1378.
17. Luo JY, Fu D, Wu YQ, Gao Y. Inhibition of the JAK2/STAT3/SOSC1 signaling pathway improves secretion function of vascular endothelial cells in a rat model of pregnancy-induced hypertension. Cell Physiol Biochem 2016; 40: 527-537.
18. Maru L, Verma M, Jinsiwale N. Homocysteine as predictive marker for pregnancy-induced hypertension-a comparative study of homocysteine levels in normal versus patients of PIH and its complications. J Obstet Gynaecol India 2016; 66: 167-171.
19. Ren Y, Wang H, Qin H, Yang J, Wang Y, Jiang S, Pan Y. Vascular endothelial growth factor expression in peripheral blood of patients with pregnancy induced hypertension syndrome and its clinical significance. Pak J Med Sci 2014; 30: 634-637.
20. Savitz DA, Danilack VA, Elston B, Lipkind HS. Pregnancy-induced hypertension and diabetes and the risk

of cardiovascular disease, stroke, and diabetes hospitalization in the year following delivery. Am J Epidemiol 2014; 180: 41-44.

21. Toshimitsu M, Nagamatsu T, Nagasaka T, Iwasawa-Kawai Y, Komatsu A, Yamashita T, Osuga Y, Fujii T. Increased risk of pregnancy-induced hypertension and operative delivery after conception induced by in vitro fertilization/ intracytoplasmic sperm injection in women aged 40 years and older. Fertil Steril 2014; 102: 1065-1070.
22. Itoh H, Sagawa N, Nanno H, Mori T, Mukoyama M, Itoh H, Nakao K. Impaired guanosine 3',5'-cyclic phosphate production in severe pregnancy-induced hypertension with high plasma levels of atrial and brain natriuretic peptides. Endocr J 1997; 44: 389-393.
23. Konig K, Guy KJ, Walsh G, Drew SM, Barfield CP. Association of BNP, NT proBNP, and early postnatal pulmonary hypertension in very preterm infants. Pediatr Pulmonol 2016; 51: 820-824.
24. Palazzuoli A, Ruocco G, Cekorja B, Pellegrini M, Del Castillo G, Nuti R. Combined BNP and Echocardiographic assessment in interstitial lung disease for pulmonary hypertension detection. Int J Cardiol 2015; 178: 34-36.
25. Cavagna L, Caporali R, Klersy C, Ghio S, Albertini R, Scelsi L, Moratti R, Bonino C, Montecucco C. Comparison of brain natriuretic peptide (BNP) and NT-proBNP in screening for pulmonary arterial hypertension in patients with systemic sclerosis. J Rheumatol 2010; 37: 2064-2070.
26. Macheret F, Heublein D, Costello-Boerrigter LC, Boerrigter G, McKie P, Bellavia D, Mangiafico S, Ikeda Y, Bailey K, Scott CG, Sandberg S, Chen HH, Malatino L, Redfield MM, Rodeheffer R, Burnett J, Cataliotti A. Human hypertension is characterized by a lack of activation of the antihypertensive cardiac hormones ANP and BNP. J Am Coll Cardiol 2012; 60: 1558-1565.
27. Mallick MP, Ray S, Medhi R, Bisai S. Elevated serum beta hCG and dyslipidemia in second trimester as predictors of subsequent Pregnancy Induced Hypertension. Bangladesh Med Res Counc Bull 2014; 40: 97-101.
28. Masuda A, Fuji T, Iwasawa Y, Nakamura K, Ohkawa R, Igarashi K, Okudaira S, Ikeda H, Kozuma S, Aoki J, Yatomi Y. Serum auto-taxin measurements in pregnant women: application for the differentiation of normal pregnancy and pregnancy-induced hypertension. Clin Chim Acta 2011; 412: 1944-1950.
29. Sahu S, Abraham R, Vedavalli R, Daniel M. Study of lipid profile, lipid peroxidation and vitamin E in pregnancy induced hypertension. Indian J Physiol Pharmacol 2009; 53: 365-369.
30. Niederdockl J, Dempfle CE, Schonherr HR, Bartsch A, Miles G, Laggner A, Pathil A. Point-of-care PT and a PTT in patients with suspected deficiencies of coagulation factors. Int J Lab Hematol 2016; 38: 426-434.
31. Dumoulin EN, Fiers L, Devreese KM. Investigation of sensitivity for coagulation factor deficiency in APTT and PT: how to perform it? Clin Chem Lab Med 2016; 54: 169-172.
32. Sakayori T, Naito S, Yoshida M, Kumano O, Kato N, Okuda M, Ieko M. Accuracy and reliability of international normalized ratio (INR) in monitoring of warfarin-comparison in the sensitivity to extrinsic coagulation factors between PT (INR) and TT (INR). Rinsho Byori 2010; 58: 779-785.
33. Errasti ME, Prospitti A, Viana CA, Gonzalez MM, Ramos MV, Rotelli AE, Caffini NO. Effects on fibrinogen, fibrin, and blood coagulation of proteolytic extracts from fruits of Pseudananas macrodontes, Bromelia balansae, and B. hieronymi (Bromeliaceae) in comparison with bromelain. Blood Coagul Fibrinolysis 2016; 27: 441-449.
34. Singh N, Pati HP, Tyagi S, Upadhyay AD, Saxena R. Evaluation of the Diagnostic Performance of Fibrin Monomer in Comparison to d-Dimer in Patients With Overt and Nonovert Disseminated Intravascular Coagulation. Clin Appl Thromb Hemost 2015.
35. Arora MM, Mishra KB, Nair V, Bhardwaj JR, Bhalwar R, Somani BL. Diagnosing disseminated intravascular coagulation in acute infection: Can We Do without Fdp & D-Dimer. Med J Armed Forces India 2002; 58: 13-17.

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