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Hematocrit and plasma albumin levels difference may be a potential biomarker to discriminate preeclampsia and eclampsia in patients with hypertensive disorders of pregnancy

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ABSTRACT

Background: We evaluated whether alterations of hemoglobin (HB), hematocrit (HCT), serum albumin level (ALB), and the difference of HCT and ALB can be used in the diagnosis of preeclampsia and eclampsia in patients with hypertensive disorders of pregnancy (HDP).
Methods: A total of 509 individuals were recruited and divided into 4 groups: Group 1, 170 healthy non–pregnant women; Group 2, 125 normal pregnant women; Group 3, 105 pregnant women diagnosed with gestational and chronic hypertension; Group 4, 109 pregnant women diagnosed as having preeclampsia and eclampsia. Data of HB, HCT, ALB, globulin (GLB) were collected at the time of a prenatal examination during the third trimester.
Results: Alterations in the HCT and the ALB levels in these groups were significantly different. Group 4 had a higher mean HCT-ALB value ($P < 0.01$), but lower ALB and GLB values compared with the other three groups. We used Groups 2 and 3 as the respective reference to draw the receiver operating characteristic (ROC) curves of HCT-ALB in Group 4, and found that the threshold values of maximum index corresponding were 12.95 and 12.65 (sensitivity > 57.0%, specificity > 98.9%), respectively.
Conclusions: The value of HCT-ALB > 12.65 might be used as a potential biomarker for the auxiliary diagnosis of preeclampsia and eclampsia in HDP.

1. Introduction

The hypertensive disorders of pregnancy (HDP) remain a major cause of maternal and fetal morbidity and mortality. Preeclampsia, by itself, is a complication in 5% to 10% of pregnancies worldwide [1–3]. The clinical characteristics of HDP are high blood pressure affecting the function and causing physical damage to multiple organs, such as heart, lung, kidney, blood and nervous system. The American College of Obstetricians and Gynecologists has classified hypertension during pregnancy into 4 categories: 1) Gestational hypertension, 2) Preeclampsia and eclampsia, 3) Chronic hypertension, and 4) Preeclampsia superimposed on chronic hypertension [4]. At the present time, the clinical diagnosis of preeclampsia is defined by finding an elevated blood pressure and/or the severity of 24-h urine protein [5]. However, proteinuria is a poor predictor of either maternal or fetal complications in women with preeclampsia [6].

The pathophysiological basis of preeclampsia and eclampsia is the injury to systemic small arteries and capillary endothelial cells, which leads to increased vascular permeability and in turn to hemoconcentration, hypoalbuminemia and edema [7,8]. Therefore, there may be an increase of hematocrit (HCT), a reduction of serum albumin (ALB), and an increase in the HCT and ALB difference in patients with preeclampsia and eclampsia. The physiological increase of plasma volume would cause changes of maternal blood components during pregnancy [9], such as a decreased hemoglobin (HB) and ALB, and an increased HCT [10]. The effects of the pregnancy-related changes in maternal HB, ALB and HCT levels on the outcome of pregnancies have been widely studied [11–14]. It was proposed that the increased HCT, HB and red cell mass in early pregnancy can be considered as a risk factor for preeclampsia [15], and the changes in HCT levels between the first half and the second half of pregnancy might suggest preeclampsia [12].

2. Materials and methods

2.1. Study subjects and ethics statement

All the subjects were enrolled in the First Affiliated Hospital of Kunming Medical University (KMU) from January 2013 to October 2015. We collected the related data of HB, HCT, ALB, GLB, height, weight and gestational situation of each participant. The diagnostic criteria of HDP

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were based on the clinical characteristics as previously reported [16] and were listed in Table 1. The subjects were divided into 4 groups: Group 1 has 170 healthy non–pregnant women who attended for a physical examination in the First Affiliated Hospital of KMU, with an age ranging from 20 to 40 y. Group 2 has 125 normal pregnant women who delivered a baby in the same hospital, with an age from 21 to 37 y. Group 3 has 105 patients who were diagnosed as having HDP, but without preeclampsia/eclampsia. These patients aged from 26 to 36 y, including 70 patients with gestational hypertension and 35 patients with chronic hypertension. Group 4 has 109 patients who were diagnosed as already having preeclampsia and eclampsia (including 6 preeclampsia, 86 severe preeclampsia and 17 eclampsia patients), with an age from 17 to 43 y (Table 2). The value of the HCT-ALB difference was calculated for each group. Pregnant women who had received blood or protein products by infusion, developed gestational moderate to severe anemia, gestational severe bacterial infection disease, intrauterine fetal death or severe liver and kidney diseases were excluded from this study.

The Ethics Committee of the First Affiliated Hospital of KMU approved the study protocol for the collection of blood samples. Written informed consent was obtained from each subject. The procedures were carried out in accordance with the approved guidelines.

Table 1
Diagnostic criteria of with the hypertensive disorders of pregnancy.

Hypertensive disorders of pregnancy	Clinical characteristics[a]
Gestational hypertension	Onset of hypertension after gestational week 20, blood pressure ≥ 140 mmHg systolic or ≥90 mmHg diastolic, and 12 weeks postpartum returns to normal, and the urinary protein test negative; patient with blood pressure ≥ 160 mmHg systolic or ≥110 mmHg diastolic was diagnosed as having severe gestational hypertension.
Chronic hypertension	Presence or history of hypertension preconception or in the first half period of pregnancy, blood pressure ≥ 140 mmHg systolic or ≥90 mmHg diastolic, and no aggravation during the gestation period; Or patient diagnosed as hypertension from 20 weeks of pregnancy and continuing past 12 weeks postpartum. Urine protein test negative.
Preeclampsia/eclampsia	*Preeclampsia*. *De novo* hypertension (blood pressure ≥ 140/90 mmHg) after gestational week 20, and new onset of one or more of the following: proteinuria ≥0.3 g/24 h or urinary protein/creatinine ratio ≥ 0.3 or random urinary protein ≥ (+) when it unable to carry out urinary protein quantitation; Urine protein test negative, but with any of the organs (heart, lung, liver, kidney *etc.*) or systems (blood system, digestive system, nervous system) involved. Blood pressure and/or urinary protein levels continue to rise. *Severe preeclampsia*. Patient with preeclampsia appear with any of the following: (1) blood pressure ≥ 160 mmHg systolic or ≥110 mmHg diastolic; (2) persistent headache, visual disturbances or other central nervous system abnormalities; (3) persistent pain of epigastrium and liver subcapsular hematoma or rupture of the liver; (4) elevated blood alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels; (5) impaired renal function: proteinuria ≥ 0.3 g/24 h; oliguria (24 h urine output < 400 ml, or hourly urine output <17 ml) or serum creatinine > 10^6 μmol/l; (6) hypoalbuminemia with ascites, pleural or pericardial effusion; (7) hematological disorders, like platelet count was persistent decline and < 100×10^9/l. and microvascular hemolysis (anemia, jaundice or elevated blood lactate dehydrogenase (LDH) levels); (8) heart failure; (9) pulmonary edema; (10) fetal growth restriction or oligohydramnios, fetal death and placental abruption. *Eclampsia*. Other signs that cannot be explained on the basis of preeclampsia, convulsions
Preeclampsia superimposed on chronic hypertension	Patients with proteinuria ≥ 0.3 g/24 h or random urinary protein ≥ (+) after gestational week 20; proteinuria before 20 weeks of pregnancy and significantly increased urinary protein excretion after gestational week 20; further increase in blood pressure and with any other feature of severe preeclampsia.

[a] Mainly based on the previously reported criteria [16].

2.2. Statistical analysis

The values of HB, HCT, ALB, GLB and HCT-ALB were presented as the mean ± SEM. The difference between two groups was compared by using the Student's *t*-test, whereas differences between three or more groups were evaluated by one-way analysis of variance (ANOVA). The ROC curves of HCT-ALB of Group 4 were prepared by using Groups 2 and 3 as the reference standard, respectively. We calculated AUC and the right index, and took the largest right index corresponding indicators to calculate the diagnostic threshold. All statistical analyses were performed by using SPSS (ver 21.0). A $P < 0.05$ was regarded as statistically significant.

3. Results and discussion

The subjects in the 4 groups under study had a similar age ($P > 0.05$; Table 2) and were from the same geographical region. There was also no statistically significant difference in the gestational age at enrolment in the subjects of Groups 2, 3 and 4 ($P > 0.05$ data not shown). Therefore, potential differences of HB, HCT and ALB among the groups might reflect the different nature of their diseases, leaving aside any genetic effect. All tested variables (HB, HCT, ALB, GLB and HCT-ALB) were normally distributed according to the Kolmogorov-Smirnov test ($P > 0.05$), except for HB level in Group 1 ($P = 0.005$). Compared with Group 1, the levels of HB, HCT and ALB were decreased and the levels of HCT-ALB were increased in Groups 2 and 3 ($P < 0.01$; Table 3). The level of HCT-ALB was also increased ($P < 0.01$; Table 3) in Group 4, which had a decreased levels of ALB. Group 4 had an increase of HB, HCT and HCT-ALB levels and a decreased ALB and GLB levels in comparison with those of Group 2 and Group 3 ($P < 0.01$; Table 3). Note that most of eclampsia patients (13/17) had a high HCT-ALB level (>12) in Group 4. When we took Group 2 and Group 3 as the respective reference to draw the ROC curves of HCT-ALB of Group 4 (See Fig. 1), we found that the AUC were 0.786 and 0.804, respectively. The cut-point of HCT-ALB values were 12.95 (with sensitivity of 57% and specificity of 99.2%) and 12.65 (with sensitivity of 58.1% and specificity of 98.9%) base on Youden index (Table 4), respectively. These results suggested that HCT-ALB levels difference might be of reasonably good sensitivity and high specificity for the diagnosis of preeclampsia and eclampsia.

During pregnancy, the maternal vascular tone is decreased and both cardiac output and blood volume are increased to supply enough oxygen and nutrients to the fetus and placenta [17]. Long before the formation of the placenta, the reactivity of blood vessels against angiotensin II and catecholamine is reduced. Meanwhile, the increase in endothelial prostacyclin and nitric oxide production causes a decrease in systemic vascular tone, vasodilation, a decrease of cardiac afterload and baroreceptor activation, thereby resulting in an increase in the heart rate, cardiac output, cardiac contractility and increased systemic vein transfer to artery. At the same time, changes in the renin-angiotensin-aldosterone system and the increase in secretion of cortisol and antidiuretic hormone cause an increase of blood volume to restore cardiac preload. The decreased vascular reactivity also inhibits the release of atrial natriuretic peptide [18]. As the pregnancy progresses, increased estrogen levels promote sodium retention by increasing the hepatic synthesis