Journal of
Women's Health and Gynecology

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Research Open Access

Hypoalbuminemia as a Risk Factor for Preeclampsia in the Pregnant Hypertensive Population

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Received Date: January 10, 2020 **Accepted Date:** January 20, 2020 **Published Date:** January 22, 2020

Citation: Nieves Martell-Claros (2020) Hypoalbuminemia as a Risk Factor for Preeclampsia in the Pregnant Hypertensive Population. J Womens Health Gyn 7: 1-8.

Abstract

Aim: To determine whether hypoalbuminemia is related to preeclampsia (PE) in a chronic hypertensive pregnant population (cHTN) or gestational hypertensive pregnant population (gHTN) and the plasmatic albumin level to be predictive of PE.

Methods: This is an observational, retrospective study of a clinical cohort. cHTNand gHTN women were included provided that a plasmatic albumin determination at the 32th gestational week was available. They were attended in 2 specialized reference centers.

Results: 193 pregnant patients were included (60.6% gHTN and 38.9% cHTN). 57 (29.5%) patients were evaluated due to complications: PE (25.4%), HELLP syndrome (3.6 %) and a unique case of eclampsia. An albumin level ≤ 3.3 g/dl had an adjusted RR of 1.87 (IC 95%: 1.1-3.1; p=0.01) for the development of PE. Patients with albumin level <3.3 g/dl had children with a lower birth weight (-319 gr; p<0.004) and a lower gestational age on delivery (-9.1 days, p=0.002).

Conclusions: Serum albumin level ≤ 3.3 g/dl in pregnant patients with cHTN or gHTN may be a causal factor or risk marker of PE and it could also determine the fetal weight and gestational age. More studies should be conducted in order to confirm these results.

Keywords: Preeclampsia; Hypoalbuminemia; Hypertensive states of pregnancy; gestational hypertension; chronic hypertension in pregnancy.

Abbreviations: cHTN: chronic hypertensive pregnant population; gHTN gestational hypertensive pregnant population; HDP: Hypertensive disorders in pregnancy; GH: gestational hypertension; PE: preeclampsia; AII: angiotensin II; ASA: acetyl-salicylic acid; IVF: in-vitro fecundation

Condensed Abstract

We included 193 pregnant patients, 60.6% chronic hypertensive pregnant (cHTN) and 38.9% gestational hypertensive pregnant (gHTN). 57 (29.5%) patients were evaluated due to pregnant complications. An albumin level < 3.3 g/dl had an adjusted RR of 1.87 (IC 95%: 1.1-3.1; p=0.01) for the development of PE. Patients with albumin level <3.3 g/dl had children with a lower birth weight (-319 gr; p<0.004) and a lower gestational age on delivery (-9.1 days, p=0.002).

Serum albumin level <3.3 g/dl in pregnant patients with cHTN or gHTN may be a causal factor or risk marker of PE and it could also determine the fetal weight and gestational age.

According to our results, it might be considered that a serum albumin level < 3.3 g/dl is a PE marker. Avoid of serum albumin decrease or dietetically /pharmacological replacement of albumin to maintain a level above 3.3 g/dl and osmotic pressure could prevent the evolution to PE among patients with gestational or chronic arterial hypertension and maternal/fetal situations that might be associated. A number of clinical trials should be initiated to confirm these data.

Introduction

Hypertensive disorders in pregnancy (HDP) is a major cause of maternal and prenatal morbidity and mortality. It is associated with an 18% of maternal mortality. The prevalence of HDP, gestational hypertension (GH) and preeclampsia (PE) are 5.2-8.2%, 1.8-4.4% and 0.2-9.2% respectively [1].

Hypoalbuminemia is a clinical condition that is characterized by a decrease in serum levels of albumin, below 3.5 g/dl. Albumin is the main circulating protein, responsible of the 60% total plasmatic protein mass. Hypoalbuminemia drives to a decline in plasmatic oncotic pressure and it generates extravasation and edema what leads to hypovolemia.

Hypovolemia stimulates renin secretion by the kidneys, so driving to a plasmatic angiotensin I release, converting to angiotensin II (AII) and finally obtaining aldosterone secretion and a subsequent blood pressure increase.

In normal pregnancy, hemodynamic modifications are made: peripheral vascular resistance reduction, blood pressure decrease, cardiac output increase and volume expansion occurs [2]. At the end of the pregnancy, 6 to 8 liters of water are retained among the fetus, amniotic liquid and intra-extracellular spaces [3].

On the other hand, pregnant patients with PE have increase in vascular resistance and reduction in cardiac output and hypertension are developed. Proteinuria and plasmatic extravasation drive to a decrease in effective intravascular plasmatic volume and cause a decrease in central and venous filling pressure and also a decline in cardiac output [4]. Vascular peripheral resistance increase can be a secondary compensation of the reduction of cardiac output and circulating blood volume [5]. In patients with gestational hypertension but without proteinuria, plasmatic volume is not decreased [6].

Guidelines on pregnancy hypertensive states published by the Canadian Obstetric and Gynecologist Society consider a plasmatic albumin level < 2 g/dl as a criterion of severity, based on a number of studies that included non-pregnant women (threshold for edema development) and expert opinion due to a lack of more robust evidence. However, the guidelines conclude that ´the pre-term birth rate, preeclampsia severity and time of hospitalization were higher among the patients with an albumin level < 2 g/dl. Moreover, the newborn mean weight was lower in this group [7].

There are a scarce number of clinical studies about the most accurate maternal serum albumin level as a predictor of PE. According to Brown *et al.* [8], a decreased albumin level is associated with severe PE and an increase of perinatal mortality, although some studies did not confirm this correlation [9]. In fact, Gojnic *et al.* [10] concluded that serum albumin level is correlated to the PE severity and the whole population of pregnant with an albumin below 3 g/dl developed severe PE. Nevertheless, in a study conducted by Witlin *et al.* [11], which hypothesis was that a serum albumin < 3 g/dl was a PE predictor, a statistical significance was not found.

Objective

To determine whether hypoalbuminemia is related to PE in a chronic hypertensive pregnant population (cHTN) or gestational hypertensive pregnant population (gHTN) and the plasmatic albumin level to be predictive of PE.

Methods

This is a retrospective and observational study of a clinical cohort. Pregnant women with a diagnosis of chronic or gestational hypertension were included provided that a serum albumin measurement in the 32th gestational week was available. Also, the population at study needed a complete follow-up until delivery.

132 patients were included in the Gestational Hypertension Unit (Hospital Clínico San Carlos, Madrid, Spain) and 61 women at the High Obstetric Risk Unit (Hospital de Clínicas Dr. Manuel Quintela, Montevideo, Uruguay) throughout the period between March 2004 and September 2009.

Primary variable was PE while secondary variables were child weight at birth and gestational age at delivery. Independent variables were plasmatic uric acid, blood pressure, preventive treatment with acetyl-salicylic acid (ASA), age, first pregnancy, twin pregnancy, in-vitro fecundation (IVF), hematocrit, and serum albumin level. According to *Seong* y cols. [12], we chose an albumin level threshold of ≤3.3 g/dl, due to its high sensitivity and specificity level in order to differentiate PE from chronic or gestational hypertension. Besides, it is the limit to diagnose hypoalbuminemia according to the normal universal range of 3.4-5.4 g/dl.

Chronic hypertension was defined as a pre-existing hypertension prior to the 20th week. Gestational hypertension was defined as a blood pressure ≥ 140 mmHg and/or ≥90 mmHg measured twice at least in a 6 hours period, detected after the 20th week, proteinuria<0.3 g/24h and subsequent normalization following the delivery. If proteinuria was absent, severe PE was defined by a BP level ≥ 160 and/or ≥110 mmHg plus the appearance of one of the following: headache, hepatic disease with an increase in liver enzyme levels and persistent pain in the right hypochondrium, novel visual or cerebral disturbances, serum creatinine rise above 1.1 mg/dl or doubling of serum creatinine in absence of acute renal disease, thrombocytopenia <100.000 cell/mcroL, oliguria o lung edema. Eclampsia was defined as the presence of seizures after the diagnosis of arterial hypertension [13]. HELLP syndrome was defines as the diagnosis of hemolysis (microangiopathic anemia plus schistocytes), increase of liver enzymes (doubling the normal range) and platelet reduction <100.000 cell/mcroL.

Statistical analysis

Qualitative variables are described as their frequency distribution. Quantitative variables are summarized along with their mean and standard deviation (SD) or median and interquartile range (IQR) for variables without a normal distribution. Comparison of qualitative variables, according to albumin level (≤3.3 vs > 3.3 gr/dl) was performed via the χ^2 test or the Fisher test if required.

For quantitative variables with a normal distribution, Student T test was used while independent groups. If the variables were asymmetric, the non-parametric U Mann-Whitney test was used. The model of regression log-binomial was preferred with the aim of evaluating the effect of the albumin level (≤3.3 vs > 3.3 gr/dl) on the binary result variable. In order to select variables to adjust the model, they were selected after the confirmation of a statistical significance p<0.01 and/or clinical relevance between the groups under study. Hazard ratio (HR) and its 95% confidence interval (CI) are presented. The null hypothesis was refused with a type I error or alpha error below 0.05 in every hypothesis contrast. The software used was STATA for Windows v. 12.0.

Results

193 patients were included, with a mean age of 32.1±6.24 years old and range of 14-47 years. 75% were Caucasian, 2.6% black and 20.2% mestizo. 61.1% of the population developed gestational hypertension and 38.9% chronic hypertension. 57 patients (29.5%) suffered some complication: 25.4% PE, 3.6% HELLP syndrome, and a single case of eclampsia. 31.6% were primiparous and 24.9% had a background of PE. 28.5% had history of diabetes, 5 (8.6%) were type 1 diabetics, 13 (22.4%) were type 2 diabetics and 40 (69%) developed gestational diabetes. There were 9 (4.6%) twin pregnancies and 14 IVF. (Table 1).

Family history of hypertension, diabetes, dyslipidemia, preeclampsia, and eclampsia was no statistically different between groups.

Table 1 and 2 show the baseline clinical data comparison between patients with serum albumin of ≤ 3.3 g/dl y >3.3 g/dl.

Characteristics	Complete sample (n=193)	Albumin≤3.3 gr/dl (n=58)	Albumin>3.3gr/dl (n=135)	p
Age	32,1± 6.24	33.7±6.5	31.4±6	0.021
Nuliparous (n=18)	31.6%	25.9%	34.1%	0.261
Twin pregnancy (n=9)	4.6%	8.6%	3%	0.131
In vitro fecundation(n=14)	7.3%	18.6%	5.1%	0.007
Previous PE	25.0%	22.4%	26.1%	0.586
Previous E	3.1%	0.0%	4.3%	0.173
Previous DM	28.5%	34.5%	25.9%	0.227
Type 1 (n=5)	8.6%	13.6%	5.6%	0.178
Type 2 DM (n=13)	22.4%	31.8%	16.7%	
Gestational DM (n=40)	69%	54.5%	77.8%	
Caesarean section	48.4%	56.9%	44.8%	0.123
Chronic HTN	39%	50%	34.3%	0.041
Gestational HTN	61%	50%	65.7%	
Weight gain (Kg) up to 32th week	10.54±6	12±5.8	10±6.145	0.95
APGAR test	8.63±1.2	8.49±1.1	8.69±1.3	0.04

Table 1. Characteristics and background of the population of the study
PE: preeclampsia. E: eclampsia, DM: diabetes mellitus, HTN: hypertension

Characteristics	Complete sample(n=193)	Albumin≤3.3 gr/dl (n=58)	Albumin>3.3gr/dl (n=135)	p
Hematocrit (mg/dl)	36.1±2.9	36.3±3	35.9±2.8	0.021
Uric acid (mg/dl)	4.6±13	5.0±1.6	4.4±1.2	0.01
SBP (mmHg)	128±17	134±15.4	125.6±17	0.007
DBP (mmHg)	82.2±12	76.4±11.7	72.8±11.8	0.02
Albuminemia (g/dl)	3.48±0.3	3.15±0.2	3.6±0.2	0.000
Proteinuria 24h (g/l)	0.48±1.09	1.0±1.7	0.3±0.1	0.000
BP-loweringtreatment	56.6%	67.2%	54.9%	0.111
Acetylsalicilicacid	27.2%	41.4%	21.1%	0.04
PE*	29.5%	43.1%	23.7%	0.006
Childbirthweight(gr)	2982±697,7	2756±726	3076±666	0.004
Gestational age at delivery (weeks)	37.4±4	36.7±2.9	38±2.4	0.002

Table 2: Analytic parameters, blood pressure, pharmacological treatment and delivery variables
*Includes: PE, HELLP syndrome and Eclampsia. BP: Blood pressure; SBP: Systolic blood pressure; DBP: Diastolic Blood pressure

Mean serum albumin in the lower albumin group (≤ 3.3 g/dl) was 3.15±0.2 and 3.6±02 among the higher serum albumin women. (p=0.001) (Table 2). Mean age was different between groups (albuminemia ≤ 3.3 g/dl: 33.7± 6.5 years vs. albuminemia>3.3 g/dl: 31.4 ± 6 years; p=0.02). We did not find differences either in primiparous percentage (25.9% vs. 34.1%)or in twin pregnancies, but a tendency in the latter (albuminemia ≤ 3.3 g/dl: 8.6% vs. albuminemia>3.3 g/dl: 3%). Cesarean birth and eutocic deliveries were similar between groups (table 1). Both hematocrit and weight gain throughout the pregnancy showed statistical difference (p=0.02) (table 2).

The group with serum albumin ≤ 3.3 g/dl were IVF more frequently (18.6% vs. 5.1%; p=0.007) as were serum uric acid, higher in the albuminemia ≤ 3.3 group (5.0±1.6 vs. 4.4±1.2; p=0.01), and supine blood pressure level (systolic blood pressure p=0.007 and diastolic blood pressure p= 0.029). (Table 2)

There were no differences with the antihypertensive treatment. ASA indication was more frequent among the patients included in the hypoalbuminemic group (41.4% in albuminemia ≤ 3.3 g/dl versus 21.1% in albuminemia >3.3 g/dl). (p=0.004). (Table 2)

Pregnant women with albuminemia ≤ 3.3 g/dl delivered children with a lower birth weight, with a mean difference of -319 gr (p = 0.004) compared with those with albuminemia >3.3 g/dl. Gestational age at delivery was also lower, with a difference of -9.1 days for patients in the first group (p =0.002). (Table 2).

A serum albumin level below < 3.3 g/dl was detected in 13 patients, 11 of whom developed PE. We also found significant differences between groups regarding urinary 24-h protein excretion as shown in table 2.

In the group with an albuminemia ≤ 3.3 g/dl, 43.1% had clinical problems (PE, eclampsia, HELLP) versus 23.7% in the groupwith albuminemia >3.3 g/dl (p=0.007). (Table 2).

A level of albuminemia ≤ 3.3 g/dl was determined to be associated with a HR1.81 (IC 95% 1.19-2.78; p=0.01) for the development of PE. On the multiple adjustment binary logistic regression analysis, after adjustment for age, twin pregnancy, IVF, type of hypertension (gestational or chronic) and prophylactic treatment with ASA, the HR was 1.87 (IC 95%: 1.1-3.1; p=0.01).

Discussion

Our study demonstrates a statistically significant association between a level of serum albumin ≤3.3 gr/dl and a greater risk of PE and a lower child birth weight and gestational age at delivery.

Percentage of PE was higher than in general population since the recruiting centers are reference hospitals for high obstetric risk [8].

Gojnic et al. [10] published that sever PE patients had serum albumin level below 3 g/dl and concluded that those values could be valuable as a severity indicator. Accordingly, we found an albuminemia level ≤ 3.3 g/dl as a variable that is related to a HR 1.87 (IC 95% 1.18 to 2.72, p=0,041) for the development of PE in high risk pregnant. In our study, albuminemia below 3 g/dl was detected in only 13 patients, 11 of whom developed PE.

Seong et al [12] showed a higher maternal-fetal morbidity among those patients with a hypoalbuminemia < 3 g/dl, also considering it a good marker of risk for PE. As serum albumin level are below 2 g/dl, the risk for ascites, HELLP syndrome and perinatal mortality is significantly increased (HR and 95% IC: 3.5 [1.5–8.1], 12 [3.1–45], y 6.1 [1.7–22], respectively). No patient had a serum albumin level < 2 g/dl in our study.

Our findings reveal that pregnant women with an albuminemia ≤ 3.3 g/dl had newborn with a lower birth weight, with a difference of 319 grams and a lower gestational age at delivery, with a difference of 9.1 days. Therefore, this serum albumin level might indicate the threshold for a higher risk for fetal outcomes.

Previous evidence have found a serum albumin level of 3.3 g/dl to disclose a high sensitivity and specificity to differentiate PE or eclampsia from cHTN o gHTN [11]. Accordingly, our data are coincident since patients with gHTN or cHTN and an albuminemia < 3.3 g/dl were related to a HR 1.87 (IC 95%: 1.1-3.1; p=0.01) for the development of PE, HELLP syndrome or eclampsia.

We found no inverse relationship between serum albumin level and PE severity accordingly with other available evidence [6], and therefore we cannot define a predictive threshold. This might be due to a low number of patients who developed severe PE in our series (7 HELLP syndrome and 1 eclampsia).

The main underlying cause to explain the significant different serum albumin level between the groups under study is urinary 24 hours protein excretion (1.0±1.7 g/24h in pregnant with serum albumin ≤ 3.3 gr/dl vs. 0.3±0.1 g/24h in pregnant with serum albumin > 3.3 gr/dl; p=0.000). This result is consistent with the published literature as well [12].

We must recognize that prophylactic use of ASA in our population was scarce because only 27.2% of the patients received it. Nevertheless, prescription was more likely among those with a serum albumin ≤ 3.3gr/dl (41.4% vs. 21.1%; p=0.04). This fact could be behind the low incidence of severe PE [13].

Fetal-placental unit expends 1 kg of protein throughout the pregnancy approximately, mostly in the last 6 months. Diet containing 1.1 g/kg/day of protein is generally recommended to cover this need. This is usually higher than non-pregnant (0.8g/kg/day) [14]. Serum albumin decreases across the normal pregnancy due to an increase in plasmatic volume and albumin metabolism [13]. In the PE pregnant with proteinuria, a progressive decrease in serum albumin is present because of an increase of protein needs, loss of protein in urine and albumin pass to the interstitial liquid due to the endothelial damage. In these patients, an increase in sensitivity to angiotensin II is present, leading to vasoconstriction and increased blood pressure [6].

In addition to the feasible hypothesis that explain the pathophysiology of PE as placental ischemia, immune disorders and/or genetic alteration, reduction in serum albumin level could be suggested as the expected pathogenic factor for PE or at least for the poor outcomes of the gHTN or cHTN patient.

Hypoalbuminemia acts as a stressor that generates an increment of GRP78 in the endoplasmic reticle driving to a reduction in the vascular endothelial growth factor (VEGF), which is involved in angiogenesis [15]. On the other hand, among women with low serum albumin level, the transport of non-esterified fatty acid from the adipose tissue to the liver might reduce the anti-toxic activity of albumin up to a threshold that expresses very low-density lipoprotein toxicity [16-20].

Elevated uric acid increase the risk of developing the pregnancy syndrome preeclampsia. While uric acid has been mainly described as a biomarker, evidence is emerging that uric acid not only predicts the development of hypertension in pregnancy, but may be part of the causal pathway. In pregnancy, hyperuricemia frequently occurs before the development of hypertension and proteinuria, and has been proposed to have a pathogenic role in the development of preeclampsia [23]. We have previously reported on the association between elevated first trimester uric acid and increased risk for development of gestational hypertension [24].

We found statistically significant differences in uric acid level between patents with higher and lower albuminemia (5.0±1.6 vs. 4.4±1.2 mg/dl; p=0.01), which confirms the published data confirming a predictive value of uric acid to predict PE [21, 22, 23], even in the first trimester of pregnancy of healthy women for the development of gHTN [24].

Weaknesses

The major limitations of our study were: (1) that the findings on the prognostic value of the hypoalbuminemia level require prospective validation and extrapolation to various ethnic groups. (2) All data are collected from the patients' charts by two different groups from different countries, and are data directly produced in the usual clinical practice. This can cause slight variations in the diagnosis of pre-eclampisa, etc. between the teams.

Strengths

Our analysis has important strengths: (1) This is a multicenter study in two hospitals on different continents. (2) 193 patients are studied that include different ethnicities: caucasics (70%), black 2.6%) and mestizo (20.2%). (3) The two participating hospitals have a specific high-risk pregnancy unit functioning for more than 15 years, with performance protocols perfectly established in the clinical routine.

Implication for physicians and future research in this field

Any degree of hypoalbuminemia has a predictive value for preeclampsia. Therefore, it would be essential that serum albumin values be monitored throughout pregnancy and kept within normal limits. Probably making changes in the diet of pregnant women (increased protein intake) or even providing protein supplement preparations, this should be investigated with prospective intervention studies.

Conclusions

In our population under study, incidence of PE/eclampsia was higher than in general population, what is expectable due to a recruitment in high-risk clinical settings. A serum albumin level ≤ 3.3 g/dl has a HR 1.87 (IC 95%: 1.1-3.1; p=0.01) for the development of PE. Patients with albuminemia ≤3.3 g/dl, had children with a lower birth weight (-395 grams) and a lower gestational age at delivery (-9.1 days).

According to our results, it might be considered that a serum albumin level ≤ 3.3 g/dl is a PE marker. Avoid of serum albumin decrease or dietetical/pharmacological replacement of albumin to a level above 3.3 g/dl and maintain osmotic pressure could prevent the evolution to PE among patients with gestational or chronic arterial hypertension and maternal/fetal situations that might be associated. A number of clinical trials should be initiated to confirm these data.

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