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Antihypertensive Treatment Decreased Serum Leptin Levels in Severe Preeclampsia during Pregnancy

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Key Words

Leptin · Preeclampsia · Pregnancy · Antihypertensive drugs

Abstract

Background: Plasma leptin levels in preeclamptic patients have been reported to be similar compared to those of normotensive pregnant women. Nonetheless, no reports have dealt with the effect of antihypertensive treatment and leptin in preeclamptic patients. ***Methods:*** The study involved three groups of a similar age, body mass index and weeks of gestation. The groups were 30 normal pregnant women and 23 pregnant women with severe preeclampsia (SPE). The SPE patients were not treated prior to admission and the treatment was a single dose of α-methyldopa or hydralazine alone or in combination. The samples were taken at random in the afternoon (isotonic saline or pharmacological treatment) and 1 h before and after the treatment was given. Leptin serum levels were determined by a commercial sandwich ELISA assay. ***Results:*** Leptin levels of the SPE group prior to the treatment were similar to the levels recorded for the normal pregnant women. However, after 1 h leptin levels were significantly higher ($p < 0.001$) in the nontreated patients (8.0 ± 1.5) compared with those treated (5.15 ± 0.9). ***Conclusion:*** These marked differences between treated and nontreated patients suggest that leptin levels may be modulated by a single antihypertensive treatment in preeclamptic patients with a discrete increase in blood pressure.

Introduction

Pregnancy-induced hypertension (PIH) is a clinical event that occurs during gestation and reverts after having given birth and is one of the main causes of death during pregnancy [1–3]. Several patients with PIH may develop HELLP (hemolysis, increased liver enzymes and low platelet count) which is a syndrome characterised by hemolysis, an increase of hepatic enzymes and thrombocytopenia [1–4]. Generally, the patients with preeclampsia are treated immediately with antihypertensive drugs and magnesium sulfate depending on the severity of hypertension [1–4] decreasing the clinical risk of severe hypertension. Several parameters [1–4] have been studied before and after treatment; however, few reports have focused on the changes in the metabolism in these patients upon pharmacological intervention.

Leptin is a hormone encoded by the *ob* gene. Its major source is the adipose tissue [5]. Its levels increase at night and circulating concentrations reflect body fat stores [6].

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Several physiological and pathological conditions may affect leptin levels. For example, (1) Butte et al. [7] have shown that leptin levels are increased in pregnant women and that its levels decrease at term, and (2) Agata et al. [8] have shown that leptin levels are increased in essential hypertension. There are, however, no clear conclusions concerning the importance of leptin levels during pregnancy and in PIH.

A previous report by Sattar et al. [9] showed that leptin levels did not differ in preeclamptic patients as compared to normal pregnancies. Interestingly, the authors did neither differentiate between mild and severe preeclampsia (SPE) nor whether there was an effect due to pharmacological treatment. Since the effect of antihypertensive drugs could affect several metabolic parameters including lipid metabolism, the aim of the present was to assess the effect of antihypertensive treatment on the levels of leptin in SPE women.

Table 1. Characteristics of the groups

	Nontreated (n = 10)	Treated (n = 13)
Body mass index[1], kg/m^2	22±2	23±2
Age, years	24±7	26±6
Systolic pressure, mm Hg	158±15	168±17
Diastolic pressure, mm Hg	98±8	104±8
Uric acid, mg/dl	5.2±2.7	5.9±1.7
Total bilirubin, mg/dl	0.5±0.2	0.6±0.2
ALT, U/l	20±9	14±4
AST, U/l	26±10	18±6
Creatinine, mg%	0.61±0.15	0.64±0.15
Platelet, mm^3	184,307±54,066	216,000±67,369
Weeks of gestation	37±3	38±3

The characteristics of the groups are represented. These characteristics include laboratory parameters (obtained in blood and serum) as well as the weeks of gestation when the samples were taken.
[1] Body mass index calculated as described previously [12, 13].

Material and Methods

The patients studied were among those admitted to the Maternity Hospital (Maternidad Concepción Palacios) of Caracas. The study was accepted by the Ethical Committee of the hospital.

We studied 23 pregnant women with SPE. Upon written consent a sample of blood was taken. The blood sample was taken between 4 and 5 p.m. 1 h before and 1 h after a single dose of antihypertensive treatment with oral α-methyldopa (Merck, Sharp & Dohme, Caracas, Venezuela) and hydralazine intravenously (Novartis, Caracas, Venezuela, in most of the cases 11/13) or no oral treatment and saline solution.

We used the classification of the hypertensive disorders of pregnancy adopted by the American College of Obstetricians and Gynecologists in 1986 [10, 11]. Blood pressure were measured by the first and fifth Kortkoff sounds with patients in the left lateral decubitus position. The blood pressure recordings were ascertained during admission, before and after starting antihypertensive or placebo treatment and immediately before blood collection. The patients that participated in the study did not have any pharmacological treatment prior to the admission and after a careful clinical evaluation they were selected.

The patients had one or more of the following: recent systolic blood pressure persistently ≥160 mm Hg, diastolic blood pressure persistently ≥110 mm Hg, proteinuria >2,000 mg/24 h (or >3+ in semiquantitative tests), increased serum creatinine levels (>177 μmol/l, 2 mg/dl) or oliguria (<500 ml/24 h), platelet count $<1 \times 10^9$/l or evidence of microangiopathic hemolytic anemia (schistocytes, increase in indirect bilirubin levels or increase in serum-free hemoglobin levels), upper abdominal pain, headache, visual disturbances or other cerebral signs. We excluded any patient with fever, infection, other chronic diseases (such as diabetes, renal disorders, cardiopathies), or patients in whom the syndromes were not clearly defined with the aforementioned criteria. A complete medical record of each patient was kept from admission to hospital discharge.

Body mass index was calculated as described by Dawes and Grudzinskas [12] and Velazco-Orellana et al. [13]. Leptin levels were assessed in serum samples using a commercial sandwich ELISA assay (R & D Systems, UK). The sensitivity of the assay was 7.8 pg/ml, the standard curve range was between 10 and 1,000 pg/ml. Specificity of the assay was 99% and inter- and intra-assay variations were less than 5%.

The results are expressed as mean ± SD. The statistical analysis performed was the unpaired Student t test. Pearson's coefficient was assessed for all the parameters studied.

Results

In table 1, the general characteristics of the population studied are represented. No differences are observed between the groups; both groups are homogeneous. On the other hand, table 2 illustrates the effect of pharmacological treatment on leptin levels in SPE patients. No differences were observed when the values of the patients before treatment were compared with normal pregnant women. In contrast, a significant decrease in leptin levels was observed in the treated SPE patients ($p < 0.001$). This difference is significant ($p < 0.001$) among groups (treated vs. nontreated and treated vs. normal pregnancy). No significant Pearson's correlation was found between any other parameters. We could not compare the effect of single or double treatment on leptin levels due to a small number of samples.

Table 2. Effect of pharmacological treatment on leptin levels in SPE patients: Comparison with normal pregnant women

	n	Before treatment	After treatment	p
Nontreated	10	8.3±0.8	8.0±1.5	NS
Treated	13	7.5±1.5	5.15±0.9	<0.001
Normal pregnancy	30	7.28±1.5	–	

Effect of the pharmacological treatment on leptin levels in SPE compared with normal pregnant women. A significant decrease in leptin levels was observed in the treated group as compared to the nontreated group. No differences were observed before treatment in the different groups compared with normal pregnant women.

Discussion

PIH includes a variety of hypertensive states which revert at puerperium. Marked metabolic changes have been observed in pregnancy and its different types of hypertension as compared to nonpregnant women [1–4]. Among these parameters lipid metabolism is also altered.

Leptin seems to provide a link between the severity and the metabolic changes that occur during pregnancy as suggested by Sattar et al. [9].

It has been postulated that leptin levels are regulated by adipose tissue and the hypothalamus. Leptin hypothalamic receptors antagonise the effect of neuropeptide Y and of cortisol [14]. One could suggest then that antihypertensive treatment affects the regulation of leptin and in consequence fat accumulation and mobilisation observed in pregnancy [9]. However, the decrease in leptin levels could be an indirect consequence of the pharmacological treatment. It is worth noting that the effect of α-methyldopa may be different from that of hydralazine. We could not differentiate between these two drugs due to ethical considerations. In another study performed with chronic hypertensive patients, in whom α-methyldopa was used for long periods of time, leptin levels were higher in those patients as compared to controls. Thus, future studies should assess the importance of antihypertensive treatment regarding leptin levels and the difference among the drugs currently used in pregnant women with PIH.

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