CorSalud 2013 Apr-Jun;5(2):221-225

CorSalud

Cuban Society of Cardiology

Letter to the Editor

Cardiocentro Ernesto Che Guevara Santa Clara Cuba

Dyslipidemia in preeclampsia syndrome

Dislipidemia en el síndrome de preemclapsia

Pedro E. Miguel Soca✉, MD; Leticia Salinas Ojeda, MD; and Isell Corella del Toro, BN

Department of Physiological Sciences. University of Medical Sciences of Holguín. Holguín, Cuba.

Este artículo también está disponible en español

ARTICLE INFORMATION

Received: December 13, 2012
Accepted: January 20, 2013

Key words: Preemclapsia, Dislipidemia, Risk factors, Pregnancy
Palabras Clave: Preemclapsia, Dislipidemia, Factores de riesgo, Embarazo

To the Editor:

We read the interesting study by Herrera-Villalobos *et al.*[1] who demonstrated that dyslipidemia is a risk factor for preeclampsia. The cross-sectional research in 50 pregnant women has some limitations as it does not describe the whole sample design: sampling method, inclusion/exclusion criteria and universe at baseline.

Of all patients, 76% were overweight or obese, which may be related to the results obtained. Central obesity, as reflected by waist circumference, is a reliable and inexpensive indicator of atherosclerosis, cardiovascular risk and metabolic syndrome[2-3]. This visceral fat is resistant to insulin, resulting in increased flux of fatty acids to the liver via the portal vein with two immediate consequences: hepatic esteatosis occurs due to the increase of triglycerides synthesis and the formation of very low density lipoproteins (VLDL) also increases, which in turns increases blood levels of triglycerides[4].

Hypertriglyceridemia is also favored by low activity of lipoprotein lipase, an insulin-dependent endothelial enzyme, which removes chylomicrons from circulation (transporters of dietary triglycerides) and VLDL, and whose activity is low in patients with insulin resistance[5].

Hypertriglyceridemia affects the pattern of lipoproteins by increasing the activity of cholesterol ester transfer protein, an enzyme that transfers triglycerides from VLDL to the high density lipoproteins (HDL) and cholesterol esters in the opposite way, which causes HDL to become enriched with triglycerides and VLDL with cholesterol. The latter are more atherogenic and tend to form small and dense low-density lipoproteins (LDL) which are also more dangerous because of their tendency to infiltrate the intima of the arterial walls, to suffer oxidation and to be removed by receptors mechanisms of macrophage disposal and not by normal removal mechanisms through LDL receptors[6].

Meanwhile, HDL with large triglyceride content is more easily removed by hepatic lipase, which reduces plasma levels and causes an increased risk of atheros-

✉ *PE Miguel Soca*
Ave. Lenin Nº 4, esquina a Aguilera, Holguín 80500
Holguín, Cuba.
E-mail address: soca@ucm.hlg.sld.cu

clerosis. The main cardioprotective effect of these lipoproteins lies in the reverse transport of cholesterol as they move the excess of cholesterol from the arterial walls and tissues to the liver, facilitating its biliary excretion and it explains the higher cardiovascular risk in patients with low levels of HDL in blood[5,7]. However, in the research analyzed[1], there were no significant differences between the mean values of HDL between normotensive women and preeclampsia patients, which could be due to other factors not included in the study and also that patients were young of childbearing age.

The increase in blood pressure figures is due to the role of uric acid and the renin-angiotensin-aldosterone system (RAAS)[8]. Although the elevation of uric acid is considered secondary to obesity and stress, some studies suggest that this compound may have a causal role because the blocking of uricase enzyme in hyperuricemic animals develops hypertension. A mechanism that develops this disease in hyperuricemic rats is RAAS stimulation and decreased endothelial synthesis of nitric oxide[8]. In addition to its powerful vasoconstrictive effect, angiotensin II increases the systemic vascular resistance via stimulation of the sympathetic nervous system and increases blood volume due to the retention of salt and water secondary to aldosterone production and the stimulation of antidiuretic hormone.

Angiotensin II also has a proatherogenic effect by damaging the vascular endothelium, increasing oxidative stress, favoring the endothelial proliferation of smooth muscle cells and monocytes, activating platelets and inhibiting fibrinolysis, besides increasing the resistance to insulin by direct action on its receptors[8].

Maternal factors involved in hypertension during pregnancy are well described by Herrera-Villalobos *et al.*[1]. These authors refer to the atherogenic index as the total cholesterol/HDL-cholesterol ratio, whose elevation ≥ 4 increases the risk of atherosclerosis and coronary heart disease. However, other authors describe other indexes as the LDL-cholesterol/HDL-cholesterol and triglycerides/HDL-cholesterol ratios, also useful in the assessment of cardiovascular risk[9].

REFERENCES

1. Herrera-Villalobos JE, Sil Jaimes PA, Pinal González FM, Garduño Alanís A, Santamaría Benhumea AM, Rueda Villalpando JP. Índice aterogénico como factor de riesgo para el síndrome de preemclapsia. CorSalud [Internet]. 2012 [citado 11 Dic 2012];4(4): [aprox. 5 p.]. Disponible en: http://bvs.sld.cu/revistas/cors/pdf/2012/v4n4a12/es/iaterogenico.pdf
2. Castellanos González M, Benet Rodríguez M, Morejón Giraldoni AF, Colls Cañizares Y. Obesidad abdominal, parámetro antropométrico predictivo de alteraciones del metabolismo. Finlay [Internet]. 2011 [citado 10 Dic 2012];1(2):[aprox. 8 p.]. Disponible en: http://www.revfinlay.sld.cu/index.php/finlay/issue/view/7/showToc
3. Tarragó Amaya E, Miguel Soca PE, Cruz Lage LA, Santiesteban Lozano Y. Factores de riesgo y prevención de la cardiopatía isquémica. Correo Científico Médico [Internet]. 2012 [citado 10 Dic. 2012];16(2): [aprox. 16 p.]. Disponible en: http://www.revcocmed.sld.cu/index.php/cocmed/article/view/505/69
4. Miguel Soca PE. Evaluación de la resistencia a la insulina. Aten Primaria. 2010;42:489-90.
5. Miguel Soca PE, Ortigoza Garcell RI. Riesgo cardiovascular en el síndrome metabólico. Rev Cubana Cardiol Cir Cardiovasc [Internet]. 2012 [citado 12 Dic 2012];18(1):[aprox. 2 p.]. Disponible en: http://www.revcardiologia.sld.cu/index.php/revcardiologia/article/view/204/228
6. Terán-García M, Després JP, Tremblay A, Bouchard C. Effects of cholesterol ester transfer protein (CETP) gene on adiposity in response to long-term overfeeding. Atherosclerosis. 2008;196(1):455-60.
7. Miguel Soca PE. El síndrome metabólico: un alto riesgo para individuos sedentarios. Acimed [Internet]. 2009 [citado 11 Dic 2012];20(1):[aprox. 8 p.]. Disponible en: http://scielo.sld.cu/pdf/aci/v20n2/aci07809.pdf
8. Miguel Soca PE. La hipertensión arterial en el síndrome metabólico. Hipertensión. 2010; 27(4): 175-6.
9. Santiago Martínez Y, Miguel Soca PE, Ricardo Santiago A, Marrero Hidalgo MM, Peña Pérez I. Caracterización de niños y adolescentes obesos con síndrome metabólico. Rev Cubana Pediatr [Internet]. 2012 [citado 9 Dic 2012];84(1):[aprox. 8 p.]. Disponible en: http://scielo.sld.cu/pdf/ped/v84n1/ped02112.pdf

Dyslipidemia in preeclampsia syndrome. Reply
Dislipidemia en el síndrome de preemclapsia. Respuesta

To the Editor:

We appreciate the letter from Miguel Soca *et al*. and their interest in our article; and it has encouraged us to give some comments.

The cross-sectional study was conducted in two highly specialized hospitals. The sample design was non-probabilistic and sequential, according to opportunity and convenience. The patients were interviewed and underwent a follow-up for the identification of risk factors and their relation to preeclampsia. The following inclusion criteria were taken into consideration: primigravid or multigravid, aged between 14 and 39 years, in the third quarter of a pregnancy with a normal evolution. Also the following exclusion criteria were considered: smoking history, comorbidities (such as diabetes mellitus, intolerance to carbohydrates, chronic hypertension, thyroid disease, heart disease, antiphospholipid antibody syndrome, systemic lupus erythematosus, renal disease, gestational diabetes, morbid obesity), patients in labor or immediate postpartum (physiologic or surgical), and patients who were under steroid treatment at admission (fetal lung maturity scheme, with complementary diagnosis of premature rupture of membranes). And the elimination criteria: not having the full clinical record for the study, diagnosis of gestational diabetes during the course of the study, having high blood pressure, diabetes or comorbidities during the immediate postpartum period, and not having signed the informed consent letter.

There are different nuances in the clinical and biochemical presentation of patients with preeclampsia syndrome. This has led to extending the study on various risk factors, in this case the atherogenic index, which is determined in the study as the ratio of total cholesterol and high density lipoprotein cholesterol (cHDL). According to Acevedo *et al*.[1], this is the equation that has higher correlation for cardiovascular risk assessment.

It is known that central obesity, shown by the abdominal circumference, is a reliable indicator of atherosclerosis, cardiovascular risk and metabolic syndrome; however, although it is a useful marker which is associated with the risk of coronary disease, in the case of the pregnant woman it is not applicable. Also, the body mass index (BMI) is not the best indicator of obesity associated with insulin resistance and cardiovascular risk in this type of patients, which explains the differences in BMI in women who develop hypertension in pregnancy and normotensive pregnant women[2]. Furthermore, although the BMI has an influence on the elevation of lipids, it was decided not to performed in our study the statistical analysis that compares the normotensive group with the preeclampsia group according to BMI, since both groups consist of pregnant overweight or obese women and the results may not be modified. The small sample size could also have an influence.

All pregnant patients have some degree of insulin resistance; however, not all of them have complications for this reason. There are studies with cut-off points associated with preeclampsia and insulin resistance ≥ 2, and with HOMA index (homeostasis model assessment) ≥ 2 or 3 to identify the degree of association between insulin resistance and preeclampsia[3,4].

The following points are considered as potential atherogenic mechanisms of insulin resistance[5]:

Direct effects
- Increased vascular matrix
- Proliferation and migration of smooth muscle
- Decreased endothelial nitric oxide production
- Increased activity of the low density lipoprotein (LDL) receptor in arterial smooth muscle cells and macrophages.

Indirect effects: Metabolic Syndrome
- Increase in blood pressure
- Atherogenic dyslipidemia
- Decreased cHDL
- Increased triglycerides
- Small dense LDL
- Postprandial hypertriglyceridemia
- Glucose intolerance
- Central obesity
- Procoagulant state

Non-causal association:
- Consequence of vascular disease and endothelial

dysfunction
- Coincidence of obesity

The cause of pregnancy-induced hypertension has not been fully determined and multiple mechanisms have been suggested to explain the process leading to its onset. Endothelial dysfunction is considered a hallmark in the pathophysiology of pregnancy-induced hypertension, and the insulin resistance syndrome has been identified as one of the factors promoting this disorder. Hyperinsulinemia promotes the release of free fatty acids by the adipocyte and its subsequent transformation to oxidized LDL, which favors the increase of the oxidative stress, which in turn is associated with inactivation of nitric oxide and endothelial dysfunction. Likewise, visceral adipose tissue responds to the release of a number of proinflammatory cytokines, such as tumor necrosis factor-alpha and interleukin-6, which also favor endothelial dysfunction. It has been shown that patients with preeclampsia have higher concentrations of these cytokines and C-reactive protein, markers that have also been described in patients with cardiovascular diseases associated with insulin resistance[1].

In normal pregnancy, there are increased levels of cholesterol, triglycerides and free fatty acids. The abnormal characteristics of lipids in insulin resistance are accentuated in women with preeclampsia or a history of this, or gestational hypertension. These abnormalities include high plasma levels of triglycerides, free fatty acids, and lower serum levels of cHDL. However, in our study there was no statistically significant difference in the latter values, probably due to the sample size. Some studies suggest that these high cholesterol levels appear before, or during the first trimester of pregnancy, and are predictors of preeclampsia. Similar studies[6,7] **,** reported higher cholesterol levels early in the third trimester of pregnancy in women who subsequently were diagnosed with preeclampsia or gestational hypertension, compared with normotensive pregnant women. High levels of triglycerides and free fatty acids have also been found[6], and an increased cardiovascular risk has been shown[7,8].

Traditionally, it has been understood that the primary role of the renin-angiotensin-aldosterone system (RAAS) is the regulation of aldosterone secretion, vasoconstriction and retention of sodium and water. This concept helps us to understand the control of blood pressure in a linear fashion, that is to say, the production of renin-agiotensina causes an increase of blood pressure; however, pregnancy is an exception to this rule. In normal pregnancy, cardiac output increases very early at 5-6 weeks, and increases by 20%, with a secondary fall of plasma osmolality and of systemic vascular resistance and an increase in the activity of the RAAS, for a retention of water and sodium with a consequent increase of the circulating volume. According to Hernández Pacheco[9], in 1975, Ronald W. studied the RAAS in pregnancy and concluded that in normal pregnancy there is an increase of the three components of this system, which remain high during the three trimesters. In 1995, Phyllis August continued these studies and demonstrated the existence of increased renin levels in pregnancies with a normal evolution. Al Kadi *et al*.[10], in 2005, conducted a study where they measured the activity of renin and angiotensinogen in early pregnancy, as well as in the follicular phase before pregnancy, which confirmed the very early elevation of RAAS activity; an interesting fact that confirms the increase in RAAS activity as an extension of the luteal phase of the menstrual cycle. In the same study, they found high levels of renin and angiotensinogen until 36 weeks of pregnancy. How to interpret this discrepancy? Then, why pregnant women do not have high blood pressure?

The answer is the presence of angiotensin (1-7). Its main functions includes the activation of mechanisms that generate peripheral vasodilatation and antitrophic effects, amplifies the vasodilator effects of bradykinin, reduces the release of norepinephrine and actives the vasodilator system of nitric oxide – cyclic GMP. In addition, it stimulates the prostacyclin-bradykinin-nitric oxide system. The angiotensin-converting enzyme-2 (ACE-2) seems to be the point of divergence between the vasodilator function of angiotensin (1-7) and vasoconstrictor function of angiotensin II. The concentrations of ACE-1 and ACE-2 determine the vasodilator or vasoconstrictor functions of RAAS, and ACE-2 seems to have greater ability to convert angiotensin II into angiotensin (1-7)[9,10].

Thus, it is currently understood that RAAS activation occurs early in a normal pregnancy in response to hemodynamic adaptation; however, poor vascular response to the vasoconstrictor effects of angiotensin II seems to be due to the counter-regulator effect of

bradykinin, nitric oxide and prostacyclin production. Besides that, the system itself has as its mechanism that of angiotensin (1-7) to perpetuate the decline in systemic vascular resistance throughout pregnancy[9].

We are grateful for the enrichment of the article, and the openness to new paths of research in preeclampsia syndrome, also for the invitation to work as a team, as we continue with this line of research and are about to finish a review, where we can consider preeclampsia as a pregnancy metabolic syndrome.

REFERENCES

1. Acevedo M, Krämer V, Tagle R, Corbalán R, Arnaíz P, Berríos X, *et al*. Relación colesterol total a HDL y colesterol no HDL: los mejores indicadores lipídicos de aumento de grosor de la íntima media carotídea. Rev Med Chile. 2012;140(8):969-76.
2. Sierra-Laguado J, García RG, Celedon J, Pradilla LP, López-Jaramillo P. Determinación del índice de resistencia a la insulina mediante HOMA y su relación con el riesgo de hipertensión inducida por el embarazo. Rev Col Cardiol. 2006;12(7):459-65.
3. Girouard J, Giguere Y, Moutquin JM, Forest JC. Previous hypertensive disease of pregnancy is associated with alterations of markers of insulin resistance. Hipertensión. 2007;49(5):1056-62.
4. Herrera Villalobos JE, Sil Jaimes PA, Pinal González FM, Garduño Alanís A, Santamaría Benhumea AM, Rueda Villalpando JP. Asociación del índice de HOMA en hipertensión inducida por el embarazo. Rev Esc Med. 2012;26(2):2-6.
5. Palomer X, Pérez A, Blanco-Vaca F. Adiponectina: un nuevo nexo entre obesidad, resistencia a la insulina y enfermedad cardiovascular. Med Clin (Barc). 2005;124(10):388-95.
6. Solomon CG, Seely EW. Hypertension in pregnancy: A manifestation of the insulin resistance Syndrome? Hypertension. 2001;37(2):232-9.
7. Lampinem KH, Rönnback M, Groop PH, Kaaja RJ. A relationship between insulin sensitivity and vasodilation in women with a history of preeclamptic pregnancy. Hypertension. 2008;52(2):394-401.
8. Palomer X, Pérez A, Blanco-Vaca F. Adiponectina: Un nuevo nexo entre la obesidad, resistencia a la insulin y enfermedad cardiovascular. Med Clin (Barc). 2005;124(10):388-95.
9. Hernández Pacheco JA, Estrada Altamirano A. Diagnóstico y tratamiento de la Hipertensión en el embarazo. 1ra ed.. México: Prado; 2009.
10. Al Kadi H, Nasrat H, Broughton Pipkin F. A prospective, longitudinal study of the renin-angiotensin system, prostacyclin and thromboxane in the first trimester of normal human pregnancy: association with birthweight. Hum Reprod. 2005;20(11):3157-62.

Javier E. Herrera Villalobos, MD
Critical Care Unit in Obstetrics at Maternity Hospital of Social Security Institute of Mexico State, and Research Unit at Mónica Pretelini Sáenz Maternal-Perinatal Hospital.
E-mail address: je_herrera44@hotmail.com