Study on the association of hypertriglyceridemia with hypertensive states of pregnancy

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Abstract

Background: Preeclampsia occurs in 8% of pregnancies and generates 25% of perinatal deaths. Although its etiology is multifactorial, some metabolic alterations are associated with the endothelial dysfunction present in the disease, and its study could identify early markers of damage. **Objective:** To determine the relationship between plasma concentration of triglycerides in pregnant patients with hypertensive disease induced by pregnancy. **Methods:** Prospective study that included 147 healthy pregnant women and 120 women with hypertensive disease induced by pregnancy. Total cholesterol, low-density lipoprotein, high-density lipoprotein, Hemoglobin A1c, triglycerides, BH, QS, serum electrolytes, serum nitrites and liver function tests were determined. **Results:** A significant difference was found in the concentration of triglycerides between normotensive and patients with preeclampsia (261.22 ± 80.27 vs. 361.46 ± 135.17 mg/dl, $p < 0.0008$). In addition, a lower serum concentration of nitrites was observed in patients with preeclampsia, which helps explain vasoconstriction. **Conclusions:** We found an association between hypertriglyceridemia and the presence of diabetes mellitus II with the development of hypertensive disease induced by pregnancy.

KEY WORDS: Hypertriglyceridemia. Preeclampsia. Pregnancy.

Introduction

Preeclampsia is a syndrome of unknown etiology characterized by the presence of hypertension and proteinuria that appears after the 20th week of gestation¹. There are four hypertensive disorders associated with pregnancy: gestational hypertension, preeclampsia-eclampsia, chronic hypertension and chronic hypertension plus over-aggregated preeclampsia¹.

The incidence of preeclampsia is 6-8%, and it constitutes one of the world's leading causes of maternal and fetal morbidity and mortality¹. About 20-25% of all perinatal deaths are due to preeclampsia; in addition, it constitutes one of the main causes of intrauterine growth restriction in the newborn and infant morbidity and mortality due to prematurity¹.

Although endothelial dysfunction is the most commonly recognized cause in the pathophysiology of preeclampsia, its origin has not yet been established. Some risk factors associated with preeclampsia have been described, with nulliparity, age older than 35 years, obesity, chronic diseases such as chronic systemic hypertension, systemic lupus erythematosus, diabetes mellitus (DM), antiphospholipid antibodies syndrome, multiple pregnancy, trophoblast disease, African-origin ethnicity and elevated serum homocysteine concentrations standing out^{1,2}. There are several theories that try to explain preeclampsia, including placental ischemia, very low density lipoprotein-mediated cytotoxicity, genetic factors and nutritional factors. Among all of them, endothelial dysfunction can be established as a common binding tie².

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The main mechanism of endothelial damage is mediated by reactive oxygen species, i.e., superoxide radicals, which are not only produced by phagocytic cells but also by other cell populations. In pregnancy, trophoblast ischemia is known to generate superoxide radicals; an excess of these radicals produces toxicity by oxidative conversion of unsaturated fatty acids of the cell membrane, leading to uncontrolled lipid peroxidation, which generates trophoblasts sublethal cell injury and, consequently, to the endothelium that contains them, in addition to generating tumor necrosis factor alpha (TNF- α) release. The latter induces endothelial cell activation and increased expression of neutrophil and platelet adhesion molecules with a consequent release of enzymes and metalloproteinases; in addition, TNF- α stimulates the production of platelet-derived growth factor, endothelium mitogenic activity and increased cytokine release, which contribute to increase the endothelial lesion and reduce nitric oxide adequate synthesis³.

The interest in studying the endothelium in patients with preeclampsia-eclampsia starts when it is no longer considered an inert structure between blood and vascular smooth muscle due to the endothelium relaxing factor, which is nitric oxide, an inorganic free gas, the most potent modulator of cell activity that is known; it inhibits platelet aggregation, relaxes perivascular smooth muscle and acts as a neurotransmitter^{2,3}.

Increased triacylglycerol plasma levels have been described in uncomplicated pregnancy; this increase can reach up to 200 to 400% in relation to pre-gestational levels. Pregnancy can be divided in 2 stages: 1) anabolic, due to maternal hyperphagia and adipose tissue lipogenesis predominantly during the first two quarters of pregnancy, where sufficient necessary reserves are obtained for the accelerated fetal growth that will occur in the last quarter, and 2) catabolic, predominating in the third trimester, where the fetus uses previously formed fatty deposits. This is associated with the increased demands of the fetus and has as a possible consequence an increase in lipid peroxidation. There are multiple reports that refer an increase in free fatty acids concentration in the serum of pregnant patients with preeclampsia. Lipid peroxidation is a chain reaction initiated by peroxynitrite, which by eliminating a hydrogen atom from polyunsaturated fatty acids leads to the formation of hyperoxides and causes the reaction of free radicals, causing damage to the endothelium⁴.

Free radical production also generates nitric oxide deficiency by its direct destruction, as well as by an

alteration in the mechanisms that regulate its production at the endothelial level⁵.

Nitric oxide production measurement in vivo it is carried out through its metabolites, nitrites and nitrates in plasma, serum or urine⁶. The increased nitrite and nitrate levels found in patients with preeclampsia are increased directly proportionally to disease severity, which could be used as a predictor of disease severity. There is evidence suggesting that in preeclampsia there is endothelial cell dysfunction, including decreased prostacyclin (PGI₂) production (vasodilator effect), as well as an increase in endothelin plasma levels⁷.

Low-density lipoproteins (LDL) III are a fraction of triacylglycerol-rich LDLs that are not easily captured by peripheral tissues, which is why they have a higher susceptibility to oxidation, to be phagocytosed by macrophages, thus promoting the formation of small and dense type III LDL: this LDL fraction favors the synthesis of thromboxanes and increases intracellular calcium in smooth muscle blood vessels, this way contributing to vasospasm and endothelial dysfunction⁷.

With these observations, and according to current evidence, it can be claimed that the lipid peroxidation that leads to a state of oxidative stress plays an important role in the development of preeclampsia, and that alterations in the lipid profile are directly involved in this process. High fatty acid plasma concentrations are known to increase oxidation in endothelial cell walls, which induces superoxide overproduction through the mitochondrial electrons transport chain, with consequent activation of pro-inflammatory pathways and inactivation of endothelial PGI₂ and nitric oxide synthase⁷. The increase in nitric oxide concentration observed in preeclampsia from L-arginine by oxide synthase is believed to have the purpose to generate vasodilation. The increase in its production could be due to a compensatory mechanism to vasoconstriction, which is characteristic in preeclampsia⁸. The purpose of the present study is to determine the relationship between triacylglycerol plasma concentration in pregnant patients with pregnancy-induced hypertensive disease.

Method

This study was carried out at the Regional Hospital Lic. Adolfo López Mateos in the Obstetric Surgery Emergency Department during the period from January 1 to December 31, 2016. After informed consent was granted by the patients, two study groups were

formed. Group 1 was composed of 147 pregnant patients who were in the second and third trimesters of pregnancy, and came to the Department for assessment (control group); group 2 was formed with 120 pregnant patients at the second and third trimester with hypertensive disease of pregnancy (mild or severe preeclampsia, chronic systemic hypertension with over-aggregated preeclampsia, gestational hypertension).

Blood samples were collected, after an 8-hour fasting. The samples were centrifuged and kept in refrigeration until their analysis. In all samples, blood count, blood chemistry, serum electrolytes, coagulation times, glycosylated hemoglobin (HbA1c), nitrites, nitrates (nitric oxide) and lipid profile (triglycerides, total cholesterol with low density lipoprotein [LDL] and high density lipoprotein [HDL] measurements) were determined. (TABLE 1) All these determinations were made by colorimetric methods using commercial kits. Determinations were also made for lactate dehydrogenase, direct and indirect bilirubin, and glutamic-oxalacetic and glutamic-pyruvic transaminases, as well as a urinalysis to determine proteinuria, in the 20 patients who had hypertension. The nitric oxide production estimate was performed by measuring plasma nitrites and nitrates, using the Griess reagent.

The results were assessed with Student's t-test for unpaired samples, using SPSS® version 18.0. A p-value < 0.05 was considered statistically significant.

Results

The comparison of baseline parameters showed no differences between groups. Age distribution was determined for both groups (28.41 ± 6.72 years in the control group and 32.09 ± 5.78 in the study group). Cholesterol serum values (232.78 ± 63.15 for the control group and 222.03 ± 62.11 for the study group), were found to have no statistical significance ($p > 0.75$). This observation was made extensive for both high-density lipoprotein values (45.10 ± 27.33 in the control group and 41.69 ± 23.03 in the study group; $p > 0.79$) and LDL values (133.92 ± 58.11 for the control group and 140.66 ± 63.12 for the study group ($p > 0.78$)).

A really interesting result was the one obtained with triglyceride plasma concentrations. The control group showed an average value of 261.22 ± 80.27 vs. 361.46 ± 135.17 mg/dL in the study group. The difference between both reached a p-value < 0.0008. In an attempt to try to determine if the hypertensive disease stage was correlated with triglyceride concentration,

Table 1. Comparison of results in both groups by laboratory results

Parameter	Control group n = 147	Group with HDP n = 120
Age	28.41	32.09
Total cholesterol (mg/dL)	232.78	222.03
HDL (mg/dL)	45.10	41.69
LDL (mg/dL)	133.92	140.66
Triglycerides (mg/dL)	261.22	361.46
HbA1c (%)	5.116	5.011
Nitric oxide (mM)	9.81	7.67

HDP: hypertensive disease of pregnancy; HDL: high-density lipoprotein; LDL: low-density lipoprotein; HbA1c: glycosylated hemoglobin.

an evaluation was made using these parameters and we observed that there were no statistical differences between triglyceride values and disease severity (403 ± 101 in patients with mild preeclampsia and 344.4 ± 169 in patients with severe preeclampsia). Triglyceride levels in those patients with chronic hypertension who did not develop preeclampsia were similar in comparison with the control group (232.60 ± 57.13 vs. 261.11 ± 80.03 ; $p < 0.47$).

Subsequently, the percentage of patients with pregnancy-induced hypertensive disease who had a first-line family history of diabetes and high blood pressure was assessed, with 38% of women with hypertensive disease being found to have said family history vs. only 10.6% of control group patients ($p < 0.05$). Since triglyceride elevation is an important component in the metabolic syndrome associated with DM, and given that there was trend in the observed values with regard to body mass index, although not definitive, it does lead to suspect a tendency towards this problem; therefore, we assessed triglyceride serum concentration and HbA1c in all patients. Triglyceride concentration in patients with preeclampsia with a history of DM II was 361.60 ± 89.47 vs. 257.89 ± 80.20 in subjects of the control group with a history of DM II ($p < 0.0169$). Blood glucose concentrations are known to be discreetly elevated during pregnancy and, therefore, we consider that a longer-term decompensation in the glucose metabolism could be expressed by HbA1c. The results obtained showed that there is no such antecedent, since the control group had an average value of 5.116 ± 0.609 , whereas the group with hypertensive disease of pregnancy had values of 5.011 ± 0.509 ($p > 0.78$).

One of the most important factors related to physiology and homeostasis in these patients is nitric oxide. We assessed nitrite serum concentration, as a

AQ1 Table 2. Comparison of groups by triglyceride levels

	Hypertriglyceridemia	Normal triglycerides	p
Cases	361.4	261.1	< 0.47
Controls	261.2	232.6	< 0.47

product deriving from the action of nitric oxide synthase, an enzyme that is responsible for the synthesis of nitric oxide. The results showed that patients with induced hypertensive disease of pregnancy had a concentration of $7.67 \pm 5,013$ mM vs. $9.81 \pm 5,264$ mM. These values did not reach a statistically significant difference, but they do suggest a tendency towards lower nitric oxide production in patients with preeclampsia, which may well explain the presence of hypertension in these patients. It is possible that such low values are associated with the presence of a family history of diabetes, since the results showed that patients with preeclampsia with a family history of diabetes had an average nitrite concentration of 5.64 mM vs. 8.48 ± 5.45 mM in patients without such a history. These values clearly reinforce the hypothesis that, in preeclampsia, the presence of a family history of DM II has a strong specific weight (Table 1).

Discussion

During the last decade, three cardinal observations related to the pathogenesis of preeclampsia have been detected: The first one relates to abnormal placental differentiation, invasion and vascularization. The second consists of endothelial cell dysfunction, which explains the vascular manifestations of the syndrome, which include vasospasm, proteinuria, edema, hypercoagulability and abnormal prostaglandin production. The third and most recent is the association of maternal obesity with an abnormal lipid metabolism⁹.

The determination of high triglycerides as a cause of preeclampsia applies to patients in the Mexican population since, although the causes of maternal obesity are different between the various ethnic groups, it could be that there were other not yet contemplated anomalies. The results show that, indeed, triglyceride levels in pregnant women are higher than in non-pregnant women. When evaluating pregnant women, those who had hypertensive disease of pregnancy were found to have considerably higher values than those who did not develop this pathology; however, such an important increase does not seem to be related to disease severity¹⁰.

The result confirms the hypothesis that endothelial damage secondary to obesity may be due to an increase in triglyceride plasma concentration, since there is a well-described metabolic pathway that indicates that lipid increase induces an increase in the synthesis of reactive oxygen species, which favor endothelial cell membrane lipoperoxidation. Furthermore, the increase in receptors along with nitric oxide synthesis elevation, which derives from endothelial cell damage and that is mediated by TNF and that, in addition, is considered a compensation mechanism derived from the increase in endothelin 1 synthesis secondary to endothelial damage, generates an increase in the concentration of peroxynitrites and nitrates, thus increasing endothelial dysfunction¹¹.

Adequate functioning of the endothelial cell requires the presence of glucose as a fundamental factor for energy source; it is well known that in patients with diabetes or with insulin resistance, one of the observed metabolic consequences and that is more clearly defined in the "Metabolic syndrome" concept, is serum lipid accumulation. It is also true that there is a strong family predisposition to develop preeclampsia in women whose mothers have suffered this condition. The biochemical definition of this family tendency has not yet been explained; however every day more studies appear that show an important polymorphism in methylenetetrahydrofolate reductase, which is an enzyme related to hyperhomocysteinemia, which it is a well-recognized risk factor for preeclampsia and, strangely enough, also for obesity.

It is known that in diabetes initial stages both HbA1c and vascular damage determinations still do not reflect the severity of metabolic decompensation; traditionally, values slightly above the maximum level of 120 mg/dL have not been considered to represent any glucose metabolism alteration; however, these discrete glucose concentration elevations are known to induce modifications in the expression of the constitutive and inducible glucose transporters known as GLUT, which are responsible for transporting glucose into the cell.

When glucose concentration exceeds a level of 15 mM, these transporters become saturated and it is then that the glucose excess has to be taken by other metabolic pathways, thus inducing excessive lipid formation (immediate predecessor of the metabolic syndrome). This lipid increase has to be oxidized to be eliminated by the phagocytic system; however activated phagocytes also secrete pro-inflammatory cytokines such as TNF- α , which in turn deregulates endothelial cell function. Lipid increase also triggers the

lipoperoxidation cascade, thus aggravating endothelial damage¹².

Conclusions

Patients with preeclampsia have a significant increase in triglyceride plasma concentration and an elevated body mass index, and it occurs more frequently in women with a history of DM II.

The results herein presented suggest that perhaps, in the future, triglyceride concentration might be considered as a predictive factor of preeclampsia, just as hematocrit, sodium chloride, uric acid and creatinine currently are, although further studies are required in this regard.

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