ORIGINAL ARTICLES

HYPERLEPTINEMIA AS A PROGNOSTIC FACTOR FOR PREECLAMPSIA: A COHORT STUDY

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Summary: Introduction: Leptin is an adipokine which has a direct relationship to obesity. Our aim was to measure this hormone in pregnant women at three months intervals throughout their pregnancies to determine the serum value of those who developed preeclampsia.
Material and Methods: We followed 19 women (median age 24.8 ± 5.7 years) with pre-gestational Body Mass Index (BMI) less than 25 kg/m^2, 21 (median age 26.1 ± 4.6 years) with BMI higher than 25 kg/m^2 and 16 (median age 30.9 ± 5.8 years) with Gestational Diabetes Mellitus (GDM) (median age 30.9 ± 5.8 years), recruited in the 1st trimester of pregnancy. Serum levels of leptin were measured with radioimmunoassay (RIA) technique.
Results: In the first trimester of pregnancy leptin levels showed statistically significant differences between normal weight and overweight-obese women ($p < 0.001$), diabetic women ($p < 0.05$) and the subgroup of preeclamptic women ($p < 0.001$). For those women with PGBMI ≥ 40 kg/m^2 and leptin ≥ 40 ng/ml in the second trimester, the Odds Ratio (OR) to develop preeclampsia was of 47.95% CI (4.1–527.2). Analyzing leptin values with ROC curves, the greatest area under the curve (AUC) was for leptin in the second trimester (0.773, CI: 0.634–0.911).
Conclusion: Women with morbid obesity (BMI ≥ 40 kg/m^2) had significantly higher levels of serum leptin ($p < 0.01$) and a value of 40 ng/ml of this hormone seems to be predictive of developing preeclampsia in this group of patients.

Key words: *Body mass index (BMI); Gestational diabetes; Leptin; Obesity; Overweight; Pregnancy*

Introduction

Many pregnant women are obese (body mass index (BMI) > 30 kg/m^2) and the prevalence of maternal obesity is increasing (1). Obesity in pregnancy has been linked to several adverse pregnancy outcomes, including spontaneous abortion, preeclampsia, gestational diabetes (GDM), fetal macrosomia, cesarean delivery, and wound complications post-cesarean section. GDM is defined as varying degrees of carbohydrate intolerance with onset or first diagnosis during pregnancy (2).

It is recognised that the initiation of dietary or pharmacological therapy after 24 weeks gestation is likely too late to favorably impact fetal or maternal health. Consequently, some authors have proposed the term gestational prediabetes to identify women in early pregnancy (e.g., 12 weeks gestation) at risk for developing GDM using conventional glycemic testing (3).

It is worldwide accepted that preeclampsia is a multisystem disorder characterized by pregnancy-induced or gestational hypertension and new-onset proteinuria during the second half of pregnancy and is a foremost cause of maternal death (4). Therefore, the early identification of patients with an increased risk for preeclampsia is one of the most important goals in obstetrics.

Recently, it has been suggested that impaired regulation of complex interactions among various adipokines plays an important role in the development of preeclampsia (5). For instance, elevated leptin levels may be involved in the pathogenesis of preeclampsia and be associated with the development of severe disease (6; 7). Besides, leptin gene and leptin receptor gene polymorphisms have also been implicated in the development of preeclampsia (8–10).

The aim of this study was to measure the sensibility and specificity of leptin serum levels in lean, overweight-obese and diabetic pregnant women throughout their pregnancies to determine if this hormone could serve as an early prognostic marker for preeclampsia risk.

Materials and Methods

Setting

This was a cohort study conducted in the Maternal Perinatal Hospital "Mónica Pretelini" (HMPMP) from January 1, 2009, to November 30, 2010.

Accepting an alpha risk of 0.05 and a beta risk of 0.2 in a bilateral contrast, 17 subjects per group were needed to detect a difference equal to or greater than 0.6. It was assumed a proportion of 0.035 positive cases (preeclampsia) in one of the groups. The estimation of loses was of 0.1 (11).

Preeclampsia was diagnosed and classified according to the criteria specified by the technical bulletin of the American College of Obstetricians and Gynecologists (ACOG) and the National High Blood Pressure Education Program (NHBPEP) Working Group Report on High Blood Pressure in Pregnancy (12).

Subjects

Women were recruited at their first visit at 10–12 weeks gestation. They were asked to attend after an overnight fast and were tested between 0700 and 0900 h. Three groups of pregnant women were formed: a) normal weight (pre-gestational (PG) BMI < 25 kg/m^2), b) overweight-obese (PGBMI ≥ 25 kg/m^2) and c) hyperglycemic in the first trimester of pregnancy confirmed as GDM in women previously known to be normoglycemic.

Exclusion criteria were type 1 diabetes mellitus, chronic hypertension or twin pregnancy. Those women with incomplete medical records or less than two nutritional visits during the pregnancy were considered lost to the study.

Measures in each trimester

Anthropometric assessment

Body weight was measured in an overnight fasting status without shoes in a minimal clothing state by the use of a digital scale (Seca, Hamburg, Germany) to the nearest 0.1 kg. Height was measured using a non-stretched tape measure (Seca, Hamburg, Germany) to the nearest 0.1 cm. PGBMI was calculated as weight in kg divided by height in meters squared based on the prenatal chart or self-reported weight.

Blood pressure

Blood pressure (BP) was recorded using a standard sphygmomanometer (Riester Big Ben® Square, Germany) and appropriately sized cuff, that was changed to an electronic monitor (Mercury, Mennem Medical) in case of preeclampsia.

Laboratory

Blood samples were collected to measure albumin (mg/dl), cholesterol (mg/dl), creatinine (mg/dl), glucose (mg/dl), triglycerides (mg/dl), uric acid (mg/dl), liver enzymes (Dimension Rx L Max, Dade Behring), hemoglobin (g/dl) (Advia 120, Bayer Health) and general urine test according to standardized procedures recommended by the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC).

Serum levels of leptin (Millipore/Linco., USA, Cat. HL-8IHK) and adiponectin (Millipore/Linco., USA, Cat. # HADP-61HK) were determined by means of a double antibody radioimmunoassay (RIA) using materials and protocols supplied by the provider. For leptin, the sensitivity of the assay was 0.437 ng/ml + 2 SD (100 µl sample size), with an intraassay coefficient of variation (CV) of 3.4% to 8.3% and an interassay CV of 3.6% to 6.2%. For adiponectin the sensitivity was of 1 ng/ml, with an intraassay CV of 1.78% to 3.59%, an interassay CV of 6.9% to 9.25%, and a recovery rate of 99% to 117% for adiponectin.

Gestational diabetes test

At the time of recruitment the medical staff used the following risk factors to screen women for GDM: a first-degree relative with diabetes, a history of GDM or macrosomia, persistent glucosuria, a rapid or excessive weight gain during early pregnancy, a random plasma glucose ≥ 7 mmol/l. Women with one or more of these factors underwent the standard 100 g (Silanes Laboratory, Mexico) 3-h oral glucose tolerance test (OGTT) after an overnight fast. The diagnosis of GDM was made according to the National Diabetes Data Group (NDDG) (13).

Diet

All women were given individualized dietary advice from a qualified dietitian. Compliance with the dietary regimen was evaluated weekly during visits to the high-risk pregnancy clinic.

Statistical analysis

We used the SPSS version 16. Continuous variables were expressed in means ± standard deviation (SD). Initial data were assessed through simple crosstabulations and by using $\chi 2$ test for categorical variables. Kruskal Wallis and Mann-Whitney U tests were used as the variables were not normally distributed. Multivariable test were performed to evaluate the effect of covariates on leptin, systolic and diastolic BP. A Kaplan Meier curve was developed for censored cases of preeclampsia with leptin values above 40 ng/ml.

Receiver Operating Characteristic (ROC) curves were used with each variable and in the cases of preeclampsia. A p value ≤ 0.05 was considered statistically significant.

Ethics

This study was approved by the Ethical and Research Committee of the HMPMP, code: 2009-07-55 and registered in Clinical Trials (ID: NCT01649167). All participants provided written informed consent.

Results

Subjects

We followed 19 women of normal weight (median age 24.8 ± 5.7 years), 21 women who were overweight-obese (median age 26.1 ± 4.6 years) and 16 women with diabetes mellitus (median age 30.9 ± 5.8 years). The mean weight gain was in the ranges described by the Institute of Medicine (IOM), 10.5 ± 1.7, 6.5 ± 3.4 and 11.4 ± 6.4 kg for these three groups. Table 1 shows the baseline demographic, clinical and metabolic characteristics of the study population in pregnancy, stratified into the three gestational groups.

Tab. 1: Sociodemographic and clinical characteristics

	Normal		BMI > 25		GDM	
Cases[1]	19	33.9	21	37.5	16	28.5
Age (years)[2,b*]	24.8	5.7	26.1	4.6	30.9	5.8
Occupation1						
Home	15	79	18	85.7	14	87.5
With job	4	21	2	9.5	2	12.5
Parity[2]						
Pregnancies	1.7	0.8	2.6	1.3	2.7	1.5
Scholarity[1]						
Primary School	0	0	6	28.5	5	31.2
High School	13	68.4	10	47.6	8	50.0
College	6	31.6	4	19.0	1	6.2
University	0	0	0	0	2	12.5
Clinical measures[2]						
Pregestational weight (kg)[a,b***]	52.5	6.1	75.1	12.7	84.1	13.9
PGBMI (kg/m^2)[a,b***]	21.7	1.5	30.6	3.7	34.9	5.4
Weeks of gestation[b***]	39.3	0.7	38.4	1.9	37	2.9
Baby weight (kg)[b***]	3091.5	222.4	2946.4	493.8	2658.5	549
Preeclampsia[1]	0	0	4	19	4	25
IUGR[1]	0	0	3	14.2	5	31.25

[1] n and percentage; [2] mean ± Standard deviation; BMI: body mass index; IUGR: intrauterine growth restriction, PGBMI: pregestational body mass index. [a] (between normal weight and overweight-obese women), [b] (between normal weight and diabetic women). * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Measures

Measures with significant differences are synthesized in table 2. With the Kruskal Wallis test, we found significant statistical differences in the following variables: age, pre-gestational weight, height, PGBMI, weeks' gestation, systolic BP, diastolic BP, cholesterol (1st and 2nd trimester), glucose (1st and 2nd trimester), leptin (1st and 2nd trimester), triglycerides (1st trimester) and baby weight. There were no significant differences among the groups with respect to parity.

Tab. 2: Variables with statistically significant differences by intergroup comparisons

Variable	Trimester		
	First	Second	Third
Cholesterol (mg/dl)	c (152.6 ± 28.2 vs 176.6 ± 23.2)*	b (219.9 ± 31.4 vs 183.8 ± 45.7)* c (219.9 ± 31.4 vs 196.8 ± 17.7)**	
Systolic blood pressure (mm Hg)	a (101.3 ± 8.1 vs 111.3 ± 10.7)*** c (101.3 ± 8.1 vs 122.6 ± 11.7)***	c (109.7 ± 3.8 vs 128.7 ± 8.4)***	a (115.1 ± 3.1 vs 128.2 ± 11.1)*** c (115.1 ± 3.1 vs 145 ± 8.1)***
Diastolic blood pressure (mm Hg)	a (66 ± 4.8 vs 72.9 ± 5.8)*** c (66 ± 4.8 vs 81.2 ± 7.9)***	a (70 ± 3.3 vs 74 ± 6.7)** c (70 ± 3.3 vs 85.1 ± 13.9)***	a (76 ± 2.3 vs 85 ± 5.7)*** c (76 ± 2.3 vs 96 ± 3.7)***
Glucose (mg/dl)	a (82.1 ± 6.4 vs 87.7 ± 7.2)* b (82.1 ± 6.4 vs 113.4 ± 31)*** c (82.1 ± 6.4 vs 99.1 ± 21)***	b (79.6 ± 6.3 vs 96.4 ± 13.7)*** c (79.6 ± 6.3 vs 90.1 ± 11.4)**	b (78.1 ± 6.6 vs 93.4 ± 15.8)**
Leptin (ng/ml)	a (29.6 ± 11 vs 45.8 ± 13.1)*** b (29.6 ± 11 vs 40.3 ± 9.6)* c (29.6 ± 11 vs 46 ± 7)***	a (36.8 ± 13.9 vs 49.9 ± 15.1)* c (36.8 ± 13.9 vs 54.6 ± 5.6)**	c (38.8 ± 12 vs 55.4 ± 8.8)*
Triglycerides (mg/dl)	a (125.4 ± 27.6 vs 165.5 ± 47.9)* b (125.4 ± 27.6 vs 170.8 ± 56.7)* c (125.4 ± 27.6 vs 172 ± 59.6)***		

a (between normal weight and overweight-obese women), b (between normal weight and diabetic women), c (between normal weight and preeclamptic women).
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Comparing the results of women who were normal weight with women who were overweight-obese, the first group had lower levels of pre-gestational weight ($p < 0.001$), PGBMI ($p < 0.001$), diastolic BP (1st and 3rd trimester: $p < 0.001$, 2nd trimester: $p < 0.01$), systolic BP (1st and 3rd trimester: $p < 0.001$), glucose and triglycerides in the 1st trimester ($p < 0.05$) and leptin (1st trimester: $p < 0.001$, 2nd trimester: $p < 0.05$).

Comparing women of normal weight versus women with diabetes, the first group was younger ($p < 0.001$), reached more weeks of gestation and babys' weight ($p < 0.001$) and showed lower levels in pre-gestational weight ($p < 0.001$), PGBMI ($p < 0.001$), cholesterol (2nd trimester), glucose (1st and 2nd trimester: $p < 0.001$, 3rd trimester: $p < 0.01$), leptin (1st trimester) ($p < 0.05$) and triglycerides (1st trimester).

Between normal weight women and the subgroup of preeclamptic women, the second group was older ($p < 0.001$), reached less weeks' gestation ($p < 0.05$), and had higher values in glucose (1st trimester: $p < 0.001$, 2nd trimester: $p < 0.01$), cholesterol (1st trimester: $p < 0.001$, 2nd trimester: $p < 0.01$), leptin (1st trimester: $p < 0.001$, 3rd trimester: $p < 0.05$), pre-gestational weight, PGBMI and triglycerides (1st trimester) ($p < 0.001$).

Comparing overweight-obese women with diabetic pregnant women, the first group was younger ($p < 0.05$), reached more weeks of gestation ($p < 0.05$) and babys' weight ($p < 0.01$), had lower levels of PGBMI ($p < 0.01$),

diastolic and systolic BP ($p < 0.001$ the three evaluated periods) as well as glucose (1st trimester: $p < 0.01$, 2nd trimester: $p < 0.05$) and higher of leptin (2nd trimester) ($p < 0.05$).

Taking into account two conditionals, PGBMI $\geq$ 40 kg/m^2 and leptin $\geq$ 40 ng/ml in the second trimester, the Odds Ratio (OR) to develop preeclampsia was of 47.95% CI (4.1–527.2), $p = 0.0018$. Following this, the power to discern a difference was around 100% (proportion with the two conditionals = 80%, proportion two = 7.8%). Multivariate tests showed a lack of effect of age, parity, PGBMI and pre-gestational weight on leptin, systolic and diastolic BP in the second trimester.

During the follow-up period, there were no cases of preeclampsia in the group of pregnant women with normal PGBMI. In contrast, four patients in each of the other groups (overweight-obese and GDM) developed this complication. Kaplan Meier curve of censored cases of preeclampsia with leptin values above 40 ng/ml illustrates this behaviour (Fig. 1).

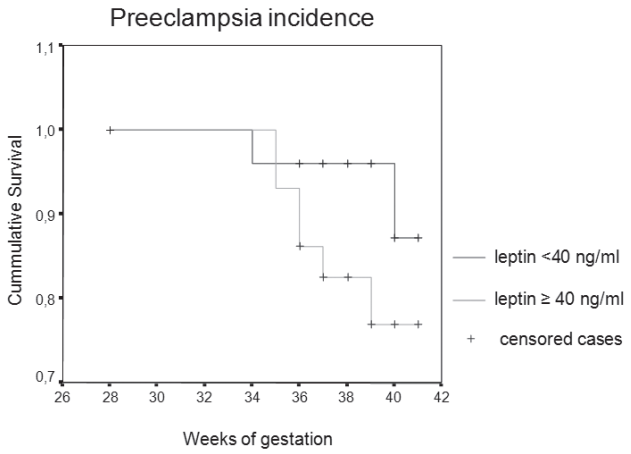

Fig. 1: Kaplan Meier curve for time to preeclampsia based upon serum leptin levels
For leptin < 40 ng/ml: Mean Survival Time (MST): 40.63 weeks, Standard Error (SE): 0.28, 95% Confidence Interval (CI) (40.08–41.19). For leptin $\geq$ 40 ng/ml: MST: 39.98 weeks, SE: 0.38, 95% CI (39.24–40.72).

With ROC curves, the greatest area under the curve (AUC) for a variable associated with preeclampsia was for final weight (0.826, CI: 0.714–938), followed by PGBMI (0.822, CI: 0.667–967) (Fig. 2). With a PGBMI value of 38.5 kg/m^2, we had a sensitivity of 0.5 and a specificity of 0.921. Analyzing leptin values with this test, the greatest AUC was for leptin in the second trimester (0.773, CI: 0.634–0.911) followed by leptin in the first trimester (0.750, CI: 0.714–0.886) (Fig. 3).

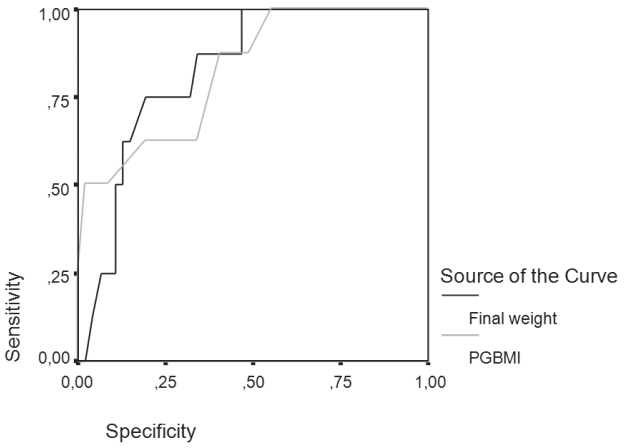

Fig. 2: Receiver Operating Characteristic (ROC) curves of final weight and pregestational body mass index
PGBMI: pre-gestational body mass index

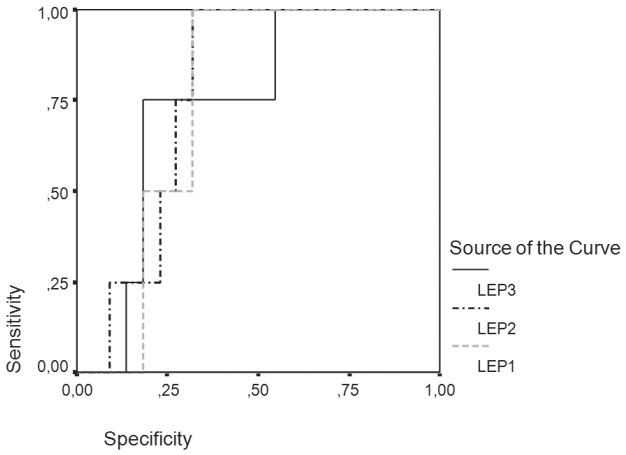

Fig. 3: Receiver Operating Characteristic (ROC) curves of serum leptin levels
Lep1: leptin in the first trimester, Lep2: leptin in the second trimester, Lep3: leptin in the third trimester

After regrouping by PGBMI, those women with morbid obesity (PGBMI $\geq$ 40) had leptin value in the first trimester of 54 ± 9 ng/ml, while those with obesity (PGBMI $\geq$ 30) had 42 ± 13.2 ng/ml and those with overweight (25 $\leq$ PGBMI < 30) had 41 ± 14.3 ng/ml.

Discussion

In our population, dietary patterns during pregnancy were similar to those previously reported for the Mexican population with substantial deficiencies in intakes of cereals, legumes and vegetables (14).

Given the weight gain during pregnancy, this physiological moment can be seen as a forced stage of over-

weight-obesity with all of the risks of this pathology. Rising levels of obesity strengthen the potentially clinical significance of our findings related to the increasing importance of first-trimester identification of women at the greatest risk for complications such as GDM or preeclampsia. In our study, higher values of systolic BP at the time of recruitment and at the end of gestation were correlated with overweight-obese women compared to normal weight women.

In support of the notion of damage produced by obesity during gestation, was the finding that two women initially followed in the overweight-obese group developed GDM. Furthermore, of the women who developed preeclampsia, four were morbidly obese (PGBMI ≥ 40), three were obese (30 ≤ PGBMI < 40) and one was overweight (25 ≤ PGBMI < 30). Of the other women, there was only one who was morbidly obese who did not develop preeclampsia.

We also searched for possible differences in the weight of babies among the groups and found that this variable was higher in normal pregnancies than in GDM. This difference is attributed to the premature interruption of pregnancies in the last group due to preeclampsia. In fact, normal pregnancies had a longer duration of gestation when compared to the GDM group. This behavior was similar when comparing overweight-obese women versus the GDM group, with a longer duration of gestation and heavier babies in the former group when compared to the latter.

Similar to Ray et al. (3), we think that the actual recommendation to screen for GDM conditions is too late for physicians to diagnose a critical metabolic problem for the mother and fetus, making it obligatory to consider new guidelines and terms. In our work, glucose in diabetic women was higher than in the other groups at the moment of admission to our study. Fortunately, we reached metabolic control after the follow-up with advice from the nutritionist. Among all of the women, there was a tendency for cholesterol, triglycerides and leptin to increase.

Due to the worldwide diversity in the results of adiponectin and pregnancy (15–18), we measured this adipokine only to characterize those women with normal weight, and the mean values for the first, second, and third trimester were 14.3, 20.6 and 43 μg/ml, respectively.

Evidence shows that maternal leptin levels correlate with maternal weight, BMI, mid-arm circumference and skinfold thickness, but not with birth weight, placental weight or maternal height (19). Controversy exists in the literature, regarding maternal leptin levels in GDM. This discrepancy could be a result of the differences in the time of maternal blood sampling (20).

Some authors have published that leptin is not associated with preeclampsia and that neither adiponectin nor leptin differ significantly between mild and severe cases (21; 22). On the contrary, previous studies have demonstrated that plasma leptin concentrations are increased significantly during the third trimester of preeclamptic pregnancies when compared to normal pregnancies (23). Even more, it has been documented that plasma leptin levels are elevated before preeclampsia becomes clinically evident (24). Our results support this late notion as leptin levels in preeclamptic patients were significantly higher compared to controls in each trimester (46 ± 7, 54.6 ± 5.6, 55.4 ± 8.8 vs. 29.6 ± 11, 36.8 ± 13.9, 38.8 ± 12) ng/ml. Unlike weight gain, leptin in pregnancy had a better AUC for cases that developed preeclampsia. Specifically, a leptin level of 40.2 ng/ml in the first trimester had a sensitivity of 0.875 and a specificity of 0.311 for developing preeclampsia. In addition, seven of eight preeclampsia cases in our cohort study had leptin reports above this level. The fact that the concentrations of leptin increased in diabetic women, despite the metabolic control reached, suggest that this adipokine is not modifiable by insulin treatment but by BMI.

There is evidence to suggest that the placenta, rather than maternal adipose tissue, makes a substantial contribution to the increase of maternal leptin concentrations (25; 26). In fact, placental leptin expression has been shown to be up-regulated by different pregnancy hormones such as chorionic gonadotrophin and 17beta-estradiol and also by second messengers such as cyclic adenosine 5′-monophosphate (27–29). Even more, the production of leptin from placental syncytiotrophoblasts increases with gestational age, leading to an increased leptin level in maternal circulation (25). Although this is a very important concept, we were not able to collect and weight the placentas as these tissues were used for other studies.

In the context of our population, the key finding of the current study is the demonstration that elevated serum levels of leptin in pregnant women in the first and second trimesters can be predictors for preeclampsia, suggesting that this hormone is an important factor contributing to this complication of pregnancy (30). Further studies are required to verify whether this hypothesis is true at an early stage of pregnancy (31). Importantly, this adipokine is not modified by insulin treatment as with adiponectin and maintains a direct relationship with visceral adiposity. This last point, "the obesity issue" (pre-gestational BMI, weight gain in pregnancy) (32), could explain at least in part the contradictory data concerning the pattern of adipocytokines' secretion in normal and complicated pregnancies.

Conclusion

Leptin values higher than 40 ng/ml in the first trimester was present in 87.5% of pregnant women with morbid obesity who developed preeclampsia. Therefore, this adipokine could be useful as a prognostic marker for preeclampsia.

Some limitations for this study may be attributed to the relatively low number of reviewed pregnancies, which did not allow to run multivariable regression models to adjust for important covariates. Beyond the previous restriction mentioned, other important adipokines were not determined in this study. Probably a larger cohort may have yielded different results.

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