ARTÍCULO ORIGINAL

Gac Méd Caracas 2025;133(3):780-790
DOI: 10.47307/GMC.2025.133.3.13

Glucose-dependent insulinotropic polypeptide (GIP) and resistin as biomarkers in preeclampsia

Polipéptido insulinotrópico dependiente de glucosa (GIP) y resistina como biomarcadores en la preeclampsia

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SUMMARY

Introduction: *The glucose-dependent insulinotropic polypeptide (GIP) is a hormone released in the small intestine in response to food intake. Its primary function is to regulate blood glucose homeostasis by stimulating insulin secretion. Preeclampsia (PE) is a syndrome exclusive to human pregnancy whose manifestations include high blood pressure, proteinuria, and edema. Its incidence increases in women with metabolic syndrome and insulin resistance. Pregnancy is a unique state characterized by physiological insulin resistance that resolves after delivery. The knowledge of the role of GIP in preeclampsia and gestational insulin resistance is scarce.* **Methods:** *Plasma levels of GIP, GLP-1, resistin and insulin were quantified in healthy pregnant women and those with PE, which belongs to a population of 30 Venezuelan women. Plasma samples were evaluated using multiplex bead analysis (Bio-Plex Pro Assays).* **Results:** *The results show significant increases in plasma levels of GIP, associated with increases in insulin and resistin levels in preeclamptic women compared to healthy pregnant women. There was a positive, statistically significant correlation between SBP and glycemia, proteinuria, resistin, GIP, and insulin.* **Conclusion:** *The results suggest that the increase in GIP and resistin could be associated with the development of hypertension and insulin resistance in patients with PE. Likewise, they indicate that the GIP and the parameters evaluated could constitute possible biomarkers to predict the appearance of pregnancy-induced hypertension and gestational diabetes.*

Keywords*: Preeclampsia, GIP, insulin resistance, gestational diabetes.*

RESUMEN

Introducción: *El polipéptido insulinotrópico dependiente de glucosa (GIP) es una hormona que se libera en el intestino delgado en respuesta a la ingesta de alimentos. Su función principal es regular la homeostasis de la glucosa sanguínea mediante la estimulación de la secreción de insulina. La preeclampsia (PE) es un síndrome exclusivo del embarazo humano, cuyas manifestaciones incluyen hipertensión arterial, proteinuria y edema. Su incidencia aumenta en mujeres con síndrome metabólico y resistencia a la insulina. El embarazo es un estado único que se caracteriza por una resistencia fisiológica a la insulina que se resuelve después del parto. Se conoce poco acerca del papel del GIP en la*

DOI: https://doi.org/10.47307/GMC.2025.133.3.13

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Recibido: 15 de abril 2025
Aceptado: 18 de julio 2025

preeclampsia y la resistencia a la insulina gestacional. **Métodos:** *Se cuantificaron los niveles plasmáticos de GIP, GLP-1, resistina e insulina en mujeres con embarazos normales y PE, pertenecientes a una población de 30 mujeres venezolanas. Las muestras de plasma se evaluaron mediante análisis de microesferas multiplex (Bio-Plex Pro Assays).* **Resultados:** *Los resultados muestran aumentos significativos en los niveles plasmáticos de GIP, asociados con aumentos de insulina y resistina en las mujeres preeclámpticas, en comparación con mujeres embarazadas sanas. Se observó una correlación positiva y estadísticamente significativa entre la PAS y la glucemia, la proteinuria, la resistina, el GIP y la insulina.* **Conclusión:** *Los resultados sugieren que el aumento del GIP podría estar asociado con el desarrollo de hipertensión y resistencia a la insulina en pacientes con PE. Asimismo, indican que el GIP y los parámetros evaluados podrían constituir posibles biomarcadores para predecir la aparición de hipertensión inducida por el embarazo y la diabetes gestacional.*

Palabras clave*: Preeclampsia, GIP, resistencia a la insulina, diabetes gestacional.*

INTRODUCTION

Incretin hormones, GIP (glucose-dependent insulinotropic polypeptide) and GLP-1 (glucagon-like peptide-1), are gut peptides released after nutrient intake, boosting insulin secretion and reducing hyperglycemia. GIP is primarily produced by K cells in the duodenum and jejunum in response to carbohydrates and fats. GIP and GLP-1 are the known incretin hormones from the upper (GIP, K cells) and lower (GLP-1, L cells) gut (1). Once released, the peptide interacts with the GIP receptor (GIPR), enhancing insulin release from pancreatic beta cells, protecting these cells from apoptosis, promoting their proliferation, and decreasing glucose production in the liver. Additionally, it reduces stomach acid secretion and improves fat storage of triglycerides in adipose tissue, thereby enhancing the tissue's sensitivity to insulin (2). GIP has also been shown to promote beta cell survival and stimulate the release of GLP-1 from islet alpha cells. Endogenous GLP-1, a 32-amino acid peptide, is secreted by L-cells in the distal small intestine and colon after nutrient ingestion, primarily carbohydrates, fats, and proteins. This secretion plays a crucial role in regulating blood glucose levels and promoting overall metabolic health. Specifically, GLP-1 stimulates insulin synthesis and secretion from pancreatic beta-cells, enhances beta-cell proliferation, inhibits beta-cell apoptosis, and reduces glucagon release from pancreatic alpha-cells (3).

Incretins GIP and GLP-1 play a key role in the incretin effect, which amplifies insulin secretion after oral glucose intake compared to intravenous glucose. In Type 2 diabetes (T2DM), this effect is diminished due to reduced GIP efficacy and a lessened role of GLP-1 (4,5). GIP plays a role in regulating pancreatic β-cell mass, which is often altered in type 2 diabetes. In T2DM, the response of β-cells to GIP can be impaired, and there may be a decrease in β-cell mass (4,6).

Preeclampsia (PE) is a pregnancy-specific syndrome characterized by new-onset hypertension and proteinuria after 20 weeks of gestation, often accompanied by edema and endothelial dysfunction. It is a leading cause of maternal and fetal morbidity and mortality worldwide (7-9). Women with pre-gestational diabetes (both type 1 and type 2) have a two to four times higher risk of developing preeclampsia (PE) compared to women without diabetes (10). Additionally, the presence of diabetes itself, especially when poorly controlled, can disrupt the normal placental development and function, increasing the risk of PE. Likewise, women with metabolic syndrome are also at high risk of suffering from PE (8). It is known that both metabolic syndrome and type 2 diabetes (11) are closely linked to insulin resistance, and pregnancy itself induces insulin resistance, particularly in the later stages, around the 20th week of gestation. This means that the body's cells become less responsive to insulin, making it harder to regulate blood sugar levels (12,13). Indeed, during pregnancy, a temporary state of insulin resistance develops as a normal physiological adaptation to support fetal development. This resistance, which resolves after delivery, is characterized by the body's reduced sensitivity to insulin, ensuring that glucose is readily available for the growing fetus. While this resistance is a natural part of pregnancy, it can sometimes become excessive, leading to complications like gestational diabetes (GDM) or, potentially, PE (14). However, the

mechanisms responsible for insulin resistance and its possible association with PE have not yet been fully clarified.

During pregnancy, maternal β-cell mass undergoes a physiological and reversible expansion to compensate for increased insulin resistance, both in animals and humans (15). Given the positive actions of the two incretins on β-cell mass, which result from the reciprocal effects on β-cell proliferation and cell death, Moffet et al. (15) examined the role of GLP-1 and GIP in the adaptation of islets to pregnancy, using mice subjected to knockout (KO) of the incretin receptor. The results revealed an important role for GLP-1 in the pregnancy-induced increase in β-cell mass, mediated mainly by the local production of GLP-1 in α-cells. In contrast, GIPR KO mice demonstrated intact mechanisms of islet adaptation to pregnancy, suggesting that islet- or K-cell-derived GIP is not essential for the pregnancy-associated expansion of β-cell mass.

Little is known about the role of GIP in preeclampsia and gestational insulin resistance. However, some studies have shown that GIP levels may be related to obesity and insulin resistance (16). Obesity and insulin resistance are known risk factors for preeclampsia.

Based on the evidence, this study aimed to quantify plasma levels of GIP, GLP-1, resistin, and insulin in women with normal pregnancies and PE and assess the possible association with the development of hypertension and insulin resistance in patients with PE. Likewise, it was of interest to establish if GIP and the parameters evaluated could constitute possible biomarkers to predict the appearance of pregnancy-induced hypertension and gestational diabetes.

MATERIALS AND METHODS

Population and Samples

A controlled experimental study was conducted in healthy pregnant women and in women with preeclampsia who met the study's inclusion criteria. Patients who attended the Gynecology Service at the Hospital Clínico Universitario de Caracas (HUC), Los Chaguaramos, Libertador Municipality, Caracas, Venezuela, were selected. The participants were pregnant women who attended the HUC obstetrics service in the emergency room and resided in the city of Caracas. The population was made up of 30 pregnant women, 16 healthy pregnant women, and 14 pregnant women with preeclampsia, aged between 17 and 40 years and with gestational ages between 28 and 40 weeks or in the last trimester of pregnancy.

The following exclusion criteria were established: chronic hypertension, autoimmune diseases, type 1 and type 2 diabetes mellitus, angiopathy, mental retardation, neurological disorders, multiple pregnancy, chronic kidney disease, patients with a body mass index (BMI) equal to or greater than 30 kg/m^2, maternal or fetal infection, and congenital anomalies of the fetus. The selected patients underwent a physical examination, and blood pressure measurements were taken. Biological samples were also collected.

All volunteers signed and dated the informed consent form in advance (before collecting the biological samples), having carefully read it. A trained staff member explained the study to them orally and in writing in a simple manner, outlining what the study entailed and what analyses would be conducted with their biological samples. Likewise, the participants clarified their doubts with the researcher in charge.

All procedures were submitted to the Bioethics Committee of the University Hospital of Caracas, Caracas, Venezuela, and complied with the Declaration of Helsinki for experimental studies involving human beings (1975, revised in 1983).

Biological samples

After fasting for 8-12 hours and without the usual prior diet, blood samples were obtained from the arm antecubital vein (left or right) by direct venipuncture in the antecubital region with multiple needles (Venojet®), using tubes with coagulation accelerator (Vacutainer®). Immediately, they were centrifuged at 3 000 rpm for 15 minutes. Plasma was separated, and aliquots were stored at -80°C until further analysis.

Blood Pressure (BP) Determination

In the supine position, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured using a mercury sphygmomanometer placed on the left arm.

Biochemical Methods

Quantification of urinary excretion of total proteins and glycemia

The colorimetric method, based on the Biuret method, was used to determine the protein concentration present in the urine through the formation of a colored chelate, resulting from a reaction between cupric ions and peptide bonds (17). The method is based on the co-precipitation of total proteins from the sample in the presence of the Ponceau red reagent and the addition of trichloroacetic acid. Briefly, the urine samples were centrifuged to eliminate tubular cells and oxalates. To 50 µL of urine, 500 µL of Ponceau red reagent (40 g/L) and trichloroacetic acid (300 g/L) were added. It was then centrifuged at 12 000 rpm for 10 minutes. The precipitate formed was resuspended by adding 1.0 mL of sodium hydroxide (8 g/L), and the concentration of urinary proteins was quantified spectrophotometrically at 560 nm. The urine protein concentration was calculated using a standard curve of bovine serum albumin at concentrations ranging from 0.125 to 8 mg/mL. The results were expressed as milligrams of protein per 100 grams of body weight.

Glycemic values were determined by enzymatic methods using the commercial kit (Stanbio). The reference values for blood glucose were 70-105 mg/dL.

Plasma adipokines quantification

All plasma samples were evaluated in duplicate using multiplex microsphere analysis (Bio-Plex Pro Assays Cytokine, Chemokine, and Growth Factors, Life Science Group, BIORAD). This technique allowed the simultaneous study of circulating concentrations of GIP, GLP-1, RANTES, Insulin, and Resistin.

Statistical analysis

The data was expressed as the mean ± standard error of the mean (S.E.M.). The data distribution was evaluated using the Shapiro-Wilk, Kolmogorov-Smirnov, and Jarque-Bera normality tests. Student's t-test and analysis of variance (ANOVA) with post-hoc analysis were used to compare the experimental groups in this study. Correlations between the variables were analyzed using the Spearman correlation test. The value of $p<0.05$ was considered significant.

RESULTS

Patient characteristics

Table 1 shows the clinical characteristics of patients. No statistically significant differences were found in age, weight, height, gestational age, or body mass index (BMI) between the two groups studied. On the contrary, significant increases in glycemia and proteinuria values were observed when comparing the two experimental groups. Similarly, SBP and DBP values were significantly higher in women with preeclampsia when compared to healthy pregnant women (Figure 1). Indeed, women with preeclampsia have been classified by an elevation in blood pressure of 20 mmHg or more, with systolic blood pressure values greater than 140 mmHg and diastolic blood pressure values greater than 78 mmHg, and a mean arterial pressure of 105 mmHg or more.

Plasma levels of adipokines and chemokines in healthy pregnant women and women with preeclampsia (pg/mL)

As shown in Table 2, under our experimental conditions, the plasma levels of GIP, resistin, and insulin increased significantly in women with preeclampsia compared to healthy pregnant women. GPL-1 peptide showed a tendency to increase, but this was not significant. In contrast, a significant reduction in plasma levels of RANTES was observed in women with preeclampsia compared to healthy controls.

Table 1. Clinical characteristics of pregnant controls and patients with preeclampsia.

Parameter	Healthy Pregnant woman	Preeclamptic woman	P
N=30	N= 16	N= 14	
Age (years)	26.47 ± 0.92	28.62 ± 2.70	NS
Weight (kg)	71.80 ± 2.97	74.24 ± 2.46	NS
Height (cm)	1.60 ± 0.02	1.59 ± 0.01	NS
BMI (kg/m^2)	28,4 ± 0,91	29.33± 0.99	NS
Gestational age (weeks)	35.5 ± 1.08 (28 - 40)	35.38 ± 0.99(29 - 41)	NS
Glycemia (mg/dL)	73.50 ± 2.46	86.23 ± 5.2*	< 0.05
Proteinuria (mg/dL)	0	4 ± 2.4 ***	< 0.0001

NS: not significative *p<0.05; ***p<0.0001 compared with control

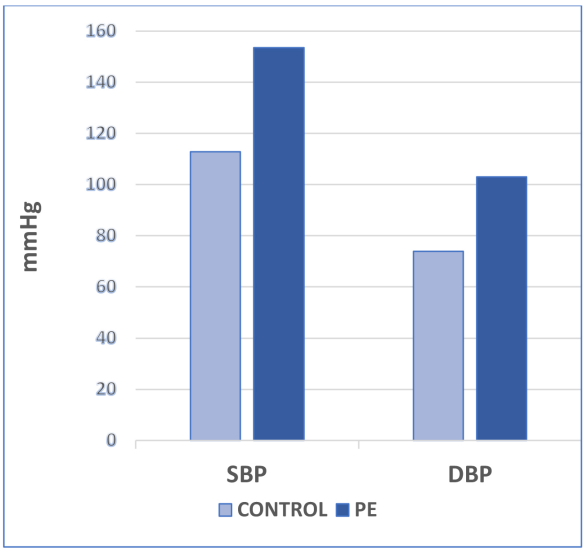

Figure 1. Blood pressure values in healthy pregnant women (CONTROL) compared to women with preeclampsia (PE). SBP (mmHg): 112.90 ± 2.26 vs. 153.58 ± 2.74 (p<0.0001). DBP (mmHg): 74.20 ± 1.81 vs. 103.16 ± 3.61(p<0.0001).

Correlation between SBP and the evaluated variables

When establishing the possible correlation between the SBP values and the evaluated variables, using the Spearman correlation test in all subjects, it was found that there is a positive, statistically significant correlation between SBP vs. proteinuria (r = 0.8192; p< 0.0001), SBP vs. glycemia (r = 0.415; p<0.0281), and SBP vs. GIP (r = 0.3755; p< 0.0489). Likewise, it is shown that SBP was positively and significantly correlated with resistin (r = 0.4410; p < 0.0166) and insulin (r = 0.4787; p <0.01). On the contrary, SBP showed a statistically significant negative correlation with RANTES (Table 3).

Table 2. Plasma levels of cytokines and chemokines in healthy pregnant women and in women with preeclampsia (pg/mL).

Parameter	Healthy pregnant women	Preeclamptic women	P
N=30	N= 16	N=14	
RANTES	115.1 ± 15.4	76.62 ± 12.48*	0.04
INSULIN	281.0 ± 138	689.49 ± 174*	0.04
RESISTIN	6 989.5 ± 1 510.51	10 304.61 ± 1 404.25*	0.04
GIP	71.9 ± 45	255.04 ± 71	0.02
GPL-1	2.6 ± 0.2	4.58 ± 1.74	NS

*p<0.05 compared with the healthy pregnant woman.

Table 3. Analysis of the Spearman correlation between SBP versus the variables evaluated in healthy pregnant women and those with preeclampsia.

	r	P
SBP vs. GLYCEMIA	0.4150	0.0281*
SBP vs. PROTEINURIA	0.8192	0.0001*
SBP vs. RESISTIN	0.4410	0.0166*
SBP vs. INSULIN	0.4787	0.0100*
SBP vs. RANTES	-0.4327	0.0215*
SBP vs. GIP	0.3755	0.0489*

DISCUSSION

The present study demonstrates the dysregulation of glucose-dependent insulinotropic polypeptide (GIP) in pregnant women with PE, whose condition was confirmed by the increase in blood pressure and proteinuria. Additionally, pregnant women with PE exhibited significant increases in plasma insulin and glucose levels. Furthermore, our findings demonstrate that the systolic blood pressure values of the pregnant patient population were positively correlated with plasma values of GIP, resistin, insulin, glycemia and with proteinuria, suggesting an association of PE with maternal insulin resistance and gestational diabetes mellitus (GDM) in the last trimester of pregnancy. Likewise, a significant negative correlation was observed between SBP and RANTES.

Preeclampsia, a common comorbidity of GDM, is characterized by endothelial dysfunction and systemic inflammation, often exacerbated by dysregulated immune signaling (16).

Glucose-dependent insulinotropic polypeptide plays a crucial role in pregnancy-related conditions such as preeclampsia and gestational diabetes mellitus (GDM). Impaired incretin response, characterized by decreased glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) activity, results in suboptimal postprandial insulin release. During pregnancy, as insulin resistance intensifies due to placental hormones (human placental lactogen, estrogen, and progesterone), the inability of β-cells to augment insulin secretion sufficiently leads to GDM (16). Lower GIP levels are inversely associated with an increased risk of GDM.

GIP has been shown to stimulate the secretion of pancreatic polypeptide, which is implicated in regulating gut motility, appetite, and glycemia. Furthermore, glycemic control, reflected by HbA1c levels, is a significant factor in the development of preeclampsia among pregnant women with diabetes, emphasizing the importance of managing glucose levels to potentially reduce the risk of preeclampsia. GIP, along with glucagon, GLP-1, VIP, and somatoliberin (also known as GHRH or growth hormone-releasing hormone), are all members of the secretin-glucagon superfamily of peptide hormones. This superfamily is characterized by its structural similarity and its ability to activate related G-protein-coupled receptors (17,18). GIP exerts its effects through a single described receptor, the GIP-R, which has 40 % and 44 % homology with the GLP-1 and glucagon receptors, respectively (18,19).

Among the effects of GIP, we must highlight its incretin activity (20,21). During fasting, GIP concentrations remain low. The ingestion of carbohydrates or fat triggers the release of GIP, increasing its plasma concentration, which in turn favors the secretion of GLP-1 from intestinal L cells. In this way, both hormones promote insulin secretion from the β-cells of the islets of Langerhans, a process known as the incretin mechanism. However, it has been demonstrated that the insulinotropic effect of GIP administration in patients with type 2 diabetes mellitus is less efficient than in healthy individuals. In this case, postprandial insulin secretion is insufficient to normalize blood glucose levels (22). Although GIP values are elevated, it appears that a reduction in sensitivity occurs in diabetic individuals due to the deficient expression of the receptor in pancreatic β-cells (23). In addition to stimulating insulin secretion, GIP exerts antiapoptotic effects and induces the growth of β-cells in the pancreas. It does this by influencing the expression of certain genes and signaling pathways that regulate cell survival. For example, GIP can increase the production of anti-apoptotic proteins, such as Bcl-2, while decreasing the production of pro-apoptotic proteins, like Bax, thereby helping to maintain a healthy beta cell population (24).

Studies on the influence of GIP on food intake are scarce and somewhat controversial. Verdich et al. (25) highlight the role of GIP in regulating appetite in humans. However, in another study, it was observed that glucose and fructose are equally effective in suppressing intake despite the large differences observed in GIP secretion in response to the administration of each saccharide (26). It has been described that GIP infusion in healthy individuals of normal weight can reduce energy expenditure and the feeling of hunger; however, this does not occur in patients with type 2 diabetes mellitus (27). In effect, whereas GLP-1 also inhibits appetite and food intake and improves glucose regulation in patients with type 2 diabetes (T2DM), GIP seems to be devoid of these activities, although the two hormones, as well as their receptors, are highly related. Numerous studies have suggested that GIP may contribute to the development of obesity (28).

Regarding the imbalance in glucose homeostasis, GIP is known to increase the secretion of resistin, a pro-inflammatory cytokine and one of the primary factors contributing to the development of insulin resistance. Studies in GIP knockout mice demonstrated a decrease in the secretion of this cytokine associated with a reduction in the development of insulin resistance after consumption of a high-fat diet (29). Resistin is a hormone secreted by monocytes, macrophages and adipocytes. Animal studies have shown that resistin induces insulin resistance and reduces glucose tolerance by inhibiting glucose uptake in the liver (30). However, the role of resistin in the physiology of pregnancy and pregnancy complications has not yet been clearly established. The present study demonstrated that increased plasma GIP levels were associated with significant increases in resistin in patients with PE compared to healthy pregnant women. Similar results were reported by Song et al. (31) and Seol et al. (32), who also demonstrated that maternal plasma resistin levels are significantly elevated in pregnant women with PE compared to normal pregnant women. However, while resistin levels are known to be elevated in PE, and GIP levels are also elevated in obesity and diabetes, the relationship between the two in PE remains poorly established. Studies indicate that resistin is elevated in PE, potentially due to impaired renal function. However, GIP's role in PE is less clear and may be more associated with

obesity and diabetes, which can be risk factors for PE (33).

Elevated GIP levels have been linked to increased mortality from cardiovascular disease in some studies. Evidence suggests that GIP, in addition to its role in regulating insulin secretion in response to glucose, also appears to be involved in the pathogenesis of cardiovascular disease, potentially influencing blood pressure and vasodilation through nitric oxide secretion, as well as vascular leukocyte adhesion and inflammation through endothelin-1 expression and secretion (34). Chronotropic and blood pressure-lowering effects of GIP have been described. In a randomized, placebo-controlled crossover study involving 10 participants with type 1 diabetes, the effect of GIP on heart rate, systolic and diastolic blood pressure was examined during hyperglycemia (plasma glucose level of 10 mmol/L) and hypoglycemia (plasma glucose levels of 3-6 mmol/L). GIP infusion during hyperglycemia increased heart rate and SBP and decreased DBP. During hypoglycemia, GIP increases heart rate and decreases DBP without altering SBP. These data suggest that the effect of GIP on heart rate is not related to its insulinotropic action since patients with type 1 diabetes lack functional residual β-cells (34). Although the interpretation of the results should be taken cautiously, the evidence suggests a possible role for GIP in regulating blood pressure. These findings would align with the results obtained in the present study, which shows an association between increased blood pressure and GIP levels in women with PE. Thus, GIP plays a role in insulin secretion and glucose metabolism, and its levels can be altered in conditions like PE, which is characterized by hypertension and other metabolic disturbances. Studies suggest that insulin resistance, a feature of PE, may be linked to higher GIP levels, and that GIP could contribute to the development of hypertension and other complications associated with PE.

PE is considered a systemic inflammatory disease, and monocyte activation is a characteristic feature of an inflammatory state. It has been demonstrated that increases in the maternal circulation of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) in PE contribute to insulin resistance and vascular dysfunction, further complicating glucose metabolism (12,16,35-40). Szarka et al. (41) demonstrated that the circulating levels of proinflammatory cytokines IL-6 and TNF-α, as well as the chemokines IL-8, IP-10, and MCP-1, and the adhesion molecules ICAM-1 and VCAM-1, are increased in PE compared to normal pregnant women, resulting in a proinflammatory systemic environment. Therefore, it can be inferred that the increased levels of the pro-inflammatory cytokine resistin observed in the present study in PE may be associated with the activation of monocytes due to a systemic inflammatory response. In addition, Hentschke et al. (42) demonstrated that RANTES expression in maternal plasma and placental tissues is higher in women with established preeclampsia compared to women with a pregnancy compatible with a healthy outcome. RANTES (Regulated upon Activation, Normal T-cell Expressed, and Secreted) // CCL5 is a chemokine that participates in diseases that cause chronic inflammation by recruiting inflammatory cells, such as leukocytes, endothelial activation, and vascular inflammation—all hallmarks of preeclampsia. It is secreted by various types of cells, including endothelial cells, smooth muscle cells, macrophages, platelets, and activated T cells. These results confirm the hypothesis that the physiology of PE is associated with an increase in the normal gestational inflammatory process. However, the results related to inflammation markers in the present study are contradictory, as decreased plasma levels of the pro-inflammatory cytokine RANTES are reported under our experimental conditions. In this regard, Taylor et al. (43) reported similar results in the levels of RANTES (In normotensive women *vs*. PE, in pg/mL, RANTES: 54.3 v*s*. 48.7). In a Venezuelan study, Reyna-Villasmil et al. (44) showed that in preeclamptic patients' RANTES concentrations were significantly higher than in healthy normotensive pregnant women, with average concentrations of 2484.6 ± 113.7 pg/mL, while healthy controls had 2002.8 ± 62.6 pg/mL, respectively. This inconsistency in RANTES results may suggest that women with PE present a unique immunological profile compared to normotensive women. However, we cannot determine whether these inflammatory markers are involved in the pathogenesis of preeclampsia and/or serve as markers of subclinical disease.

In conclusion, a circulating increase in the incretin GIP has been reported in a population of Venezuelan pregnant women at 28-40 weeks of gestation, which may play a role in the development of insulin resistance in patients with PE. These changes in circulating GIP levels and traditional risk factors will help determine the coexistence of PE and GDM. GIP plays a crucial role in pregnancy-related conditions such as preeclampsia and gestational diabetes mellitus. GIP levels are inversely associated with the risk of developing GDM, with lower GIP levels correlating with a higher likelihood of developing GDM. Overall, understanding the role of GIP in these conditions highlights its potential as a biomarker and therapeutic target in managing pregnancy-related complications, such as insulin sensitivity and resistance in PE and/or GDM. However, large-scale and prospective studies are required to assess whether the association between increased blood pressure, proteinuria, increased GIP, and other cytokines and chemokines constitutes early markers that predict the development of GDM in patients with PE.

Acknowledgments

The authors thank the Ministry of Popular Power for Science, Technology, and Innovation for subsidizing PEII Research Stimulus Project No. 20122000787.

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