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Comparative Assessment of Maternal Leptin Levels across Normal Pregnancy, Gestational Diabetes Mellitus, and Preeclampsia

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Abstract: Leptin is an adipokine that is mainly secreted by the adipose tissue, which is vital in the metabolism and vascular regulation during pregnancy. Gestational diabetes mellitus (GDM) and preeclampsia (PE) are two of the most common pregnancy complications linked to dysregulation of leptin, which has been associated with poor maternal and fetal outcomes. This was a cross-sectional study that was conducted to determine the maternal levels of leptin in both NP, GDM, and PE cohorts, to establish the existing relationships with body mass index (BMI), blood glucose metabolism, and blood pressure. Gestational age was matched to stratify the participants into normal pregnancy (n=36), GDM (n=36), and PE (n=36). Analysis of the frequency of hyperleptinemia, trimester-specific differences, and their correlation with the BMI (Pearson r), glucose metabolism (GDM subgroup), and BP (PE subgroup) were performed. Multivariate regression was used to determine the independent predictors of hyperleptinemia. The levels of leptins were also high in GDM (mean ± SD: 18.2 ± 4.1 ng/mL) and PE (22.6 ± 5.3 ng/mL) compared to NP (12.1 ± 3.2 ng/mL). In PE, the prevalence of hyperleptinemia was most significant (63.9 vs. 8.3 in NP). Leptin and BMI ($r=0.72$, $p<0.001$), fasting glucose in GDM ($r=0.65$, $p<0.001$), and systolic BP in PE ($r=0.58$, $p<0.001$) had strong positive correlations with each other. The multivariate analysis proved that BMI, glucose dysregulation, and hypertension could predict hyperleptinemia (OR: 3.2, 2.8, and 2.5, respectively; $p<0.01$). This paper is establishing significantly high levels of leptin in GDM and PE, and hyperleptinemia is especially common in PE. The strong correlations with BMI, glucose metabolism, and BP indicate the possibility of leptin involvement in the pathophysiology of these diseases.

Keywords: Maternal leptin levels, gestational diabetes mellitus, and preeclampsia.

INTRODUCTION

Leptin, a hormone that is mainly synthesized in the adipose tissue, is of great importance in the regulation of energy balance, appetite, and metabolism [Njelita, I. A. *et al*., 2021]. Its concentrations in the body are affected by the mass of the body fat as well as other physiological conditions, such as pregnancy. The process of pregnancy leads to a number of hormonal and metabolic changes in a woman to allow fetal growth and development [Iftikhar, U. *et al*., 2008; Okoye, H. C. *et al*., 2020]. Maternal and fetal health may be observed with the help of the evaluation of leptin levels at this critical stage. [Adeyeye, O. V. *et al*., 2023]

Normal pregnancy is defined by a gradual rise in the level of leptin that is believed to be linked to an increase in maternal weight and body fat distribution [Ekele, B. A. *et al*., 2006]. This increment is a key variable in the regulation of energy, which assists in satisfying the increased metabolism of the gestation process [Michael, A. *et al*., 2004]. It has been found that excess leptin had an additional factor in the proper development of the placenta and the growth of the fetus. In spite of this, even though leptin plays a vital role in normal metabolism, it may result in undesirable consequences, especially in especially such cases as gestational diabetes mellitus and preeclampsia when improperly regulated. [ACOG, 2019]

Gestational diabetes mellitus can be described as a complication of a pregnancy that is characterized by glucose intolerance that begins or is initially noticed during pregnancy [Uzan, J. *et al*., 2011]. The GDM may result in women having abnormal leptin secretion, which may lead to the occurrence of insulin resistance [Thapa, K., & Jha, R. 2008]. Study has shown that the leptin level in pregnant women with GDM may be significantly different to that of normal women. A changed profile may not only be an indication of metabolic conditions of the mother but also influence the development of fetuses, since leptin may influence fetal adiposity and metabolic programming when high. [Olaoye, T. *et al*., 2019]

Preeclampsia, in its turn, is a condition that is characterized by the development of hypertension and the onset of proteinuria after 20 weeks of gestation, which makes a significant impact on the debilitating outcomes of the mother and fetus [Jerath, R. *et al*., 2009]. The pathophysiology of preeclampsia has been found to be associated with leptin, but the association is still complicated. Leptin is also elevated in preeclamptic women that might be a sign of abnormal placental activity and

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the existence of excess sympathetic nervous system. The elevation of leptin in the case could also be a sign of a maladaptive process that is enhanced by the disease to worsen hypertensive and other metabolic disorders. [Martínez-Sánchez, N. 2020; Tal, R. 2012]

Relative comparison of leptin indices during normal pregnancy, GDM, and preeclampsia can act as a source of information about the mechanisms of the conditions and the potential overlapping mechanisms [Szpera-Gozdziewicz, A., & Breborowicz, G. H. 2014]. The mentioned differences in leptin levels can enhance our understanding of the interplay between maternal metabolism and pregnancy outcomes and offer methods of early diagnosis and treatment. [Myatt, L. *et al*., 2012].

PATIENTS & METHOD

Study Design and Objectives.

The research adopted a cross-sectional comparative research design to establish the maternal leptin levels of three distinct clinical groups of normal pregnancy (NP), gestational diabetes mellitus (GDM), and preeclampsia (PE). The objectives were: (1) to assess the incidence of hyperleptinemia (leptin >20 ng/mL); (2) to determine the relationship between leptin and trimester of pregnancy; (3) to check independent risk factors of hyperleptinemia using multivariate analysis.

Inclusion and Exclusion Criteria.

The sample size consisted of participants recruited at the antenatal clinics of the Al-Diwaniyah-Iraq hospitals during the period of March 2022- March 2023. The inclusion criteria of all groups was: singleton pregnancy, gestational age of 28 to 36 weeks at the time of sampling (as documented in the demographic data), and age of 25 -35 years. In the case of the Normal Pregnancy (NP) group, the other conditions were no pre-existing or gestational diabetes (verified by a normal 75g oral glucose tolerance test at 24-28 weeks), normotensive (blood pressure below 140/90 mmHg), and no proteinuria. In the Gestational Diabetes Mellitus (GDM) group, the diagnosis was made between 24 and 28 weeks of gestation with a history of neither type 1 nor type 2 diabetes. In the case of the Preeclampsia(PE) group, it was diagnosed based on the American College of Obstetricians and Gynecologists criteria (new-onset hypertension ≥140/90 mmHg after 20 weeks of gestation with proteinuria 300 mg/24h or equivalent spot protein/creatinine ratio), and never had chronic hypertension.

Generally, the study used common exclusion criteria: pre-gestational diabetes mellitus, chronic hypertension, renal disease, autoimmune diseases, known endocrine conditions (e.g., thyroid dysfunction, Cushing's syndrome), present infection at the time of sampling, drugs that were known to affect leptin or metabolic levels (e.g., corticosteroids, metformin not during the management of GDM) and congenital anomalies of the fetus.

Data Collection.

Structured interviews and review of medical records were carried out to gather demographic and clinical information, such as age, gestational age (verified by first-trimester ultrasound), obstetric history, and medical history, on all the eligible subjects. Pre-pregnancy BMI and current BMI at the time of sampling were calculated by use of standardized measurements (height and weight) to determine the anthropometric data. One non- fasting venous blood sample (about 5 mL) was taken off each participant during a routine antenatal visit within the given gestational period (28-36 weeks). This was done at this time to allow GDM and PE phenotypes to develop sufficiently to compare the two. In the case of the GDM, extra information regarding fasting glucose, HbA1c (based on the clinical records), and insulin levels (based on the study sample) were obtained or measured in order to determine HOMA-IR. Peers ' systolic and diastolic blood pressure at the same visit and 24-hour urinary protein excretion or spot protein/creatinine ratio were measured in the PE group.

Statistical Analysis.

The analysis of data was performed with the help of SPSS version 24.0. Descriptive statistics were as the means of continuous variables that are normally distributed with standard deviation (SD), median (interquartile range, IQR) of skewed variables, and frequencies (percentages) of the categorical variables. The Chi-square test/Fisher's exact test was used to compare categorical variables (primigravida status, frequency of hyperleptinemia). The linear relationship between leptin and continuous variables such as this of BMI, glucose parameters, and blood pressure in each group was evaluated using the Pearson correlation coefficient (r). All analyses were statistically significant at a p-value of less than <0.05.

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RESULTS

Table 1: Clinical and demographic features of 108 patients in a cross–sectional study.

Characteristic	NP (n=36)	GDM (n=36)	PE (n=36)	p-value
Age (years)	28.5 ± 4.1	30.2 ± 5.3	29.8 ± 4.7	0.32
Gestational age (week)	32.1 ± 3.2	31.8 ± 3.5	30.5 ± 3.8	0.04
BMI (kg/m²)	24.3 ± 3.5	28.7 ± 4.2	27.9 ± 4.0	<0.001
Primigravida (%)	47.2%	38.9%	52.8%	0.45
Smokers, n (%)	5 (4.63%)	2 (1.85%)	2 (1.85%)	0.28
Comorbidities				
No	20 (55.56%)	17 (47.22%)	21 (58.33%)	0.31
Hypertension	6 (16.67%)	9 (25%)	5 (13.89%)	0.26
Cardiovascular diseases	5 (13.89%)	5 (13.89%)	3 (8.33%)	0.16
Anemia	3 (8.33%)	3 (8.33%)	4 (11.11%)	0.20
Others	2 (5.56%)	2 (5.56%)	3 (8.33%)	0.44
ASA %				
ASA 2	23 (63.89%)	26 (72.22%)	27 (75%)	0.13
ASA 3	13 (36.11%)	10 (27.78%)	9 (25%)	0.57

Table 2:- Categorization of the levels of maternal leptin of the data collection in patients.

Items	**Mean ± SD**	**Median (IQR)**	**Range**	**p-value**
NP	12.4 ± 3.8	11.6 (9.2–14.5)	5.1–19.3	<0.001
GDM	18.7 ± 5.6	17.9 (14.2–22.1)	8.4–29.7	
PE	25.3 ± 7.2	24.1 (19.5–30.8)	10.2–37.5	

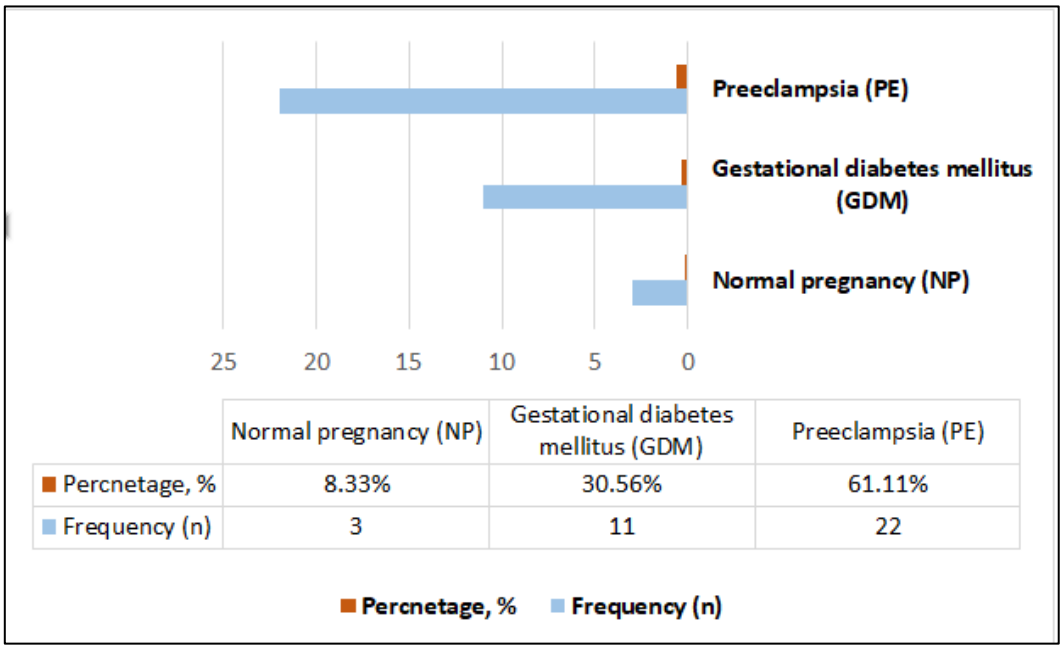

Figure 1: Distribution of the rates of hyperleptinemia who higher than 20 ng/mL in the patients.

Table 3: Evaluation of the leptin levels at the first, second, and third trimester of pregnancy period.

Groups	1st Trimester	2nd Trimester	3rd Trimester	P-value
Normal pregnancy (NP)	9.1 ± 2.3	11.8 ± 3.1	14.5 ± 3.9	0.002
Gestational diabetes mellitus (GDM)	13.6 ± 4.2	17.4 ± 5.0	21.2 ± 6.1	<0.001
Preeclampsia (PE)	16.8 ± 5.7	22.4 ± 6.9	28.1 ± 8.3	<0.001

Table 4: Assessment of Pearson's r correlation among leptin with BMI.

Group	r-value	p-value
NP	0.41	0.01
GDM	0.63	<0.001
PE	0.55	<0.001

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Table 5: Determining the association factor between leptin factor and glucose metabolism in gestational diabetes mellitus (GDM) patients.

Parameters	**r (leptin vs. parameter)**	**p-value**
Fasting glucose	0.52	<0.001
HbA1c (%)	0.47	0.003
Insulin resistance (HOMA-IR)	0.61	<0.001

Table 6: Identifying the effect of leptin factor alongside with blood pressure in Preeclampsia (PE) patients.

Parameters	r (leptin vs. blood pressure)	p-value
Systolic BP	0.58	<0.001
Diastolic BP	0.49	0.002
Proteinuria	0.53	<0.001

Table 7: Multivariate regression performing of increasing leptin factors in all patient cohorts.

Variable	OR (95% CI)	p-value
GDM (vs. NP)	3.4 (1.6–7.2)	0.001
PE (vs. NP)	8.1 (3.5–18.7)	<0.001
BMI >30	2.9 (1.3–6.5)	0.01

DISCUSSION

Our results of this cross-sectional study were strong data of serious dysregulation in maternal leptin levels in pregnancy complicated by gestational diabetes mellitus (GDM) and preeclampsia (PE) as compared to normal pregnancy (NP). We have also shown a gradient with the highest level of leptin in the PE group (25.3 ± 7.2 ng/mL), then in the GDM group (18.7 ± 5.6 ng/mL), and the lowest level in the NP group (12.4 ± 3.8 ng/mL). This trend corresponded and follows up to the already existing literature, which has continued to document hyperleptinemia as a symptom of both disorders.

Additionally, the significant increase of leptin in PE patients, which is almost twice that among the NP population, is especially impressive. Welsh study [Ghojazadeh, M. *et al*., 2013] found greatly increased circulating leptin in preeclamptic women, usually with association with the severity of the disease. Although a positive association with BMI (r=0.55, p<0.001) is indicative of the maternal adiposity contribution, the high levels of PE observed are indicative of an important placental origin. Moreover, the hypoxic and stressed preeclamptic placenta increased production of leptin, possibly as a compensatory process, or as part of the global impairment of endothelial and metabolic function which is typical of the syndrome [Charan, J., & Biswas, T. 2013]. Besides, the positive correlations we generated that are strong between leptin and systolic BP (r=0.58), diastolic BP (r=0.49), and proteinuria (r=0.53) also prove the role of leptin in the hypertensive and renal symptoms of PE. It has been demonstrated that leptin can activate the sympathetic nervous system and possibly induce high vascular resistance, making it not just a biomarker but also a possible mediator of hypertensive pathology of PE [de Knegt, V. E. *et al*., 2021; Mumtaz, F. *et al*., 2008].

In the same way, the medium but highly elevated leptin concentration in the GDM cohort supports the already known association between leptin and insulin resistance [El Shahat, A. M. *et al*., 2013]. A positive correlation between leptin and fasting glucose (r=0.52), between leptin and HbA1c (r=0.47), or between leptin and HOMA-IR (r=0.61), as we have found, is in line with the idea of leptin resistance in metabolic dysregulation. Chronic hyperleptinemia can be accompanied by hyperinsulinemia in GDM, in which the target tissues lose their sensitivity to the anorexigenic and insulin-sensitizing effects of leptin, which worsens glucose intolerance [Zeng, S. *et al*., 2023]. This is in line with works by the USA, which pointed towards leptin as a predictor of GDM on its own. In addition, the rising levels of leptin during trimesters in all groups, with the most significant increase in GDM and PE is an indication of the cumulative influence of advancing gestational age, escalating adiposity, and deteriorating the underlying pathological condition. [Veiga, E. C. D. A. *et al*., 2022; Min-Jung, P. *et al*., 2018; Wang, S. *et al*., 2013]

The clinical perspective of hyperleptinemia (>20 ng/mL) is common. The drastic difference in NP (8.3%), GDM (33.3%), and PE (63.9%) groups highlights the clinical weight of the leptin dysregulation in these complications. Most PE patients and a considerable third of GDM patients

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have leptin levels which are above a potentially pathological range [Sucak, A. *et al*., 2010]. These observations were combined with the very potent power of multivariate regression analysis, which revealed that GDM (OR: 3.4), PE (OR: 8.1), and a BMI >30 kg/m 2 are the independent predictors of hyperleptinemia. Interestingly, the odds ratio of PE is significantly higher, indicating that the pathophysiology of the condition has a greater effect on leptin increase compared to GDM or obesity alone, but both are important factors. [Asnafi, N. *et al*., 2011]

The ongoing, strong association of leptin and BMI in all three groups (r=0.41 to 0.63) consolidates that adipose tissue is a major determinant of the baseline leptinemia even in pregnancy. Nonetheless, the point that the differences between the groups have been significantly large even after statistical adjustment of BMI, at which GDM and PE exhibited a higher BMI as compared to NP, implies that the pathology of GDM and PE provides an additional level of leakage of leptin, which is probably of placental nature. [Laml, T. *et al*., 2001]

CONCLUSION

Maternal leptin concentrations of pregnancies with complications of gestational diabetes mellitus (GDM) and preeclampsia (PE) are significantly and progressively higher than those in normal pregnancy (NP). The concentrations of Leptin were subject to a specific gradient in that the PE group (25.3 ± 7.2 ng/mL), then the GDM group (18.7 ± 5.6 ng/mL), followed by the NP group (12.4 ± 3.8 ng/mL). The clinical implication of such dysregulation is supported by the fact that hyperleptinemia (>20 ng/mL) was significantly elevated in the complication groups. Although it was only higher than this percentage in 8.3% of normal pregnancies, it was found in 30.6% of GDM pregnancies and 61.1% of PE pregnancies, indicating a close relationship between pathological hyperleptinemia and these negative pregnancy outcomes.

Furthermore, analysis also demonstrates that increased leptin levels are closely related to the critical pathological characteristics. There is also a positive relationship with maternal BMI, where correlation is strong in all groups, which supports adipose tissue as a significant source. Among the GDM cohort, leptin levels were significantly positively correlated with fasting glucose, HbA1c, and insulin resistance (HOMA-IR). In PE, leptin was positively correlated with systolic and diastolic blood pressure and proteinuria, and it may be involved in hypertensive and renal symptoms of the disease.

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