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EVALUATION OF LEPTIN AS THE POTENTIAL EARLY BIOMARKER FOR GDM

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ABSTRACT

Gestational diabetes mellitus (GDM), a prevalent metabolic complication of pregnancy, poses substantial risks to both maternal and foetal well-being and serves as a harbinger for the later development of type 2 diabetes mellitus. Emerging evidence suggests that adipokines—particularly leptin, a hormone intricately involved in appetite regulation, energy balance, and insulin sensitivity—may play a pivotal role in the pathophysiology of GDM. This prospective case-control study, conducted at Janana Hospital, JLN Medical College, Ajmer, aimed to explore the predictive value of serum leptin levels in GDM and assess their relationship with key metabolic and biochemical parameters, including fasting glucose, HbA1c, HOMA-IR. A total of 260 pregnant women were enrolled and stratified into GDM cases and normoglycemic controls based on oral glucose tolerance test (OGTT) results. Our findings revealed significantly elevated leptin concentrations in the GDM group, which positively correlated with markers of insulin resistance and hyperglycaemia. These results underscore leptin's potential as a promising early biomarker for GDM, offering novel insights into risk stratification and opening avenues for timely preventative interventions.

Keywords: Gestational Diabetes Mellitus (GDM) , Leptin , OGTT , Insulin Resistance , Biomarkers.

INTRODUCTION

Gestational diabetes mellitus (GDM) refers to diabetes that often starts in the middle or late stages of pregnancy and is considered one of the most common diseases during pregnancy.[1] According to the diagnostic criteria from the International Association of Diabetes and Pregnancy Study Group (IADPSG), the incidence rate of GDM is about 13.9%.[2]

Recent years, with the prevalence of obesity, delayed childbirth, multiple pregnancies, and these factors, there is a gradual increase in GDM occurrence, with a greater impacts to the wellbeing of both mother and baby.[3]

Gestational diabetes mellitus can increase the incidence of miscarriage, premature delivery, dystocia, infection, pregnancy complications, foetal macrosomia, structural birth defects, and small for gestational age babies.[4] Gestational diabetes mellitus also significantly increases predisposition to non-GDM diabetes after pregnancy.[5] Since blood glucose screening is usually performed in the middle and late stages of pregnancy, once confirmed, there is little time for patients to receive treatment and prevent the disease from negatively impacting the foetus. Therefore, there is a need to identify some appropriate biochemical markers for the early diagnosis of GDM.

Leptin is a 16-kDa protein hormone discovered in 1994 that plays a key role in the regulation of energy intake and energy expenditure. Further, leptin is involved in a number of physiological processes including regulation of endocrine function, inflammation, immune response, reproduction and angiogenesis. Thus, it increases insulin sensitivity by influencing insulin secretion, glucose utilization, glycogen synthesis and fatty acid metabolism , regulates gonadotrophin releasing hormone secretion from the hypothalamus and activates the sympathetic nervous system. Leptin is produced mainly by adipocytes. Serum leptin levels are directly proportional to fat mass. Leptin is transported across the blood brain barrier where it binds to specific receptors of appetite-modulating neurons most notably in the arcuate nucleus.[6]

Leptin in normal pregnancy- Besides its effect on regulating gonadotrophin releasing hormone secretion, leptin plays a functional role in implantation. Moreover, it induces human chorionic gonadotrophin production in trophoblast cells, regulates placental growth, enhances mitogenesis and stimulates amino acid uptake.[7] From the earliest stages of pregnancy, maternal leptin concentrations increase implying that the increases are not only originating from maternal weight gain.[8] Circulating leptin levels reach two- to three-fold higher concentrations as compared to nonpregnant

conditions with a peak occurring around 28 weeks of gestation and a decrease to pre-gravid concentrations observed immediately after delivery.[9] Pregnancy is considered a leptin resistant state, which is associated with impaired leptin signalling in the hypothalamus.[10] One possible function of increased maternal leptin levels is to enhance the mobilization of maternal fat stores to increase avail ability and to support transplacental transfer of lipid substrates.[7] There is strong evidence that the placenta, rather than maternal adipose tissue, contributes a substantial part to the rise in maternal leptin concentrations during pregnancy.[11]

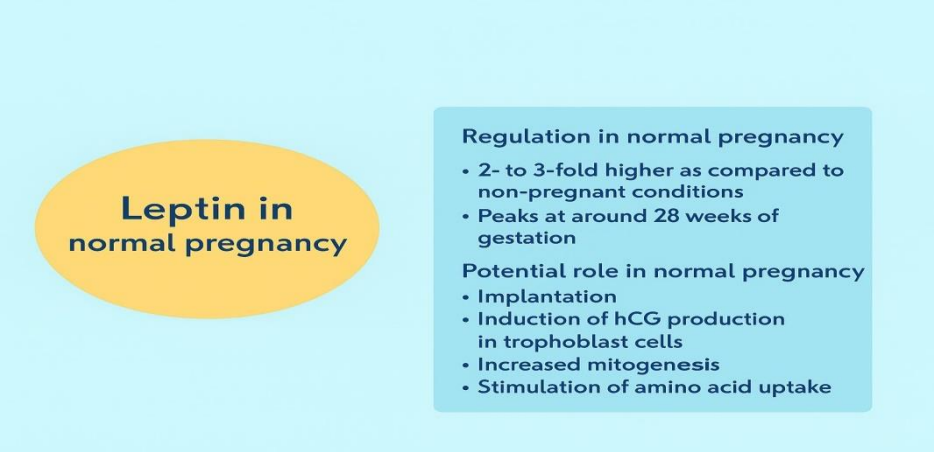


Figure 1 – showing Leptin characteristics in Normal Pregnancy.[12]

Leptin in gestational diabetes mellitus- Data on leptin in GDM have been controversial. Most studies have found increased leptin concentrations in GDM.[13] Moreover, hyperleptinaemia in early pregnancy appears to be predictive of an increased risk to develop GDM later in pregnancy independent of maternal adiposity. Furthermore, a strong linear correlation between increased maternal plasma leptin and increased risk of GDM could be observed with each 10 ng/ml increase in leptin con centration being associated with a 20% increase in GDM risk. An increase in maternal serum leptin concentrations before the onset of GDM has also been shown by other authors.[14] Gestational diabetes mellitus is characterized by an amplification of the low-grade inflammation already existing in normal pregnancy. This hypothesis is supported by increased circulating concentrations of inflammatory molecules like TNFα and IL-6 in GDM pregnancies. TNFα is one of the candidate molecules responsible for causing insulin resistance. Comparison of the placental gene expression profile between normal and diabetic pregnancies indicates that increased leptin synthesis in GDM is associated with a higher production of proinflammatory cytokines, e.g. IL-6 and TNFα causing a chronic inflammatory environment that enhances leptin production.[15] Thus, compared with normal pregnant women, placental leptin expression in patients with GDM is increased.[16] Conversely, leptin itself increases production of TNFα and IL-6 by monocytes and stimulates the production of CC-chemokine ligands.[17] Thus, a vicious circle develops, aggravating the inflammatory situation. Chronic insulin administration increases leptin secretion by adipocytes.[18] Thus, hyperinsulinaemia in GDM might further stimulate leptin production. Elevated leptin concentrations in turn amplify inflammation.

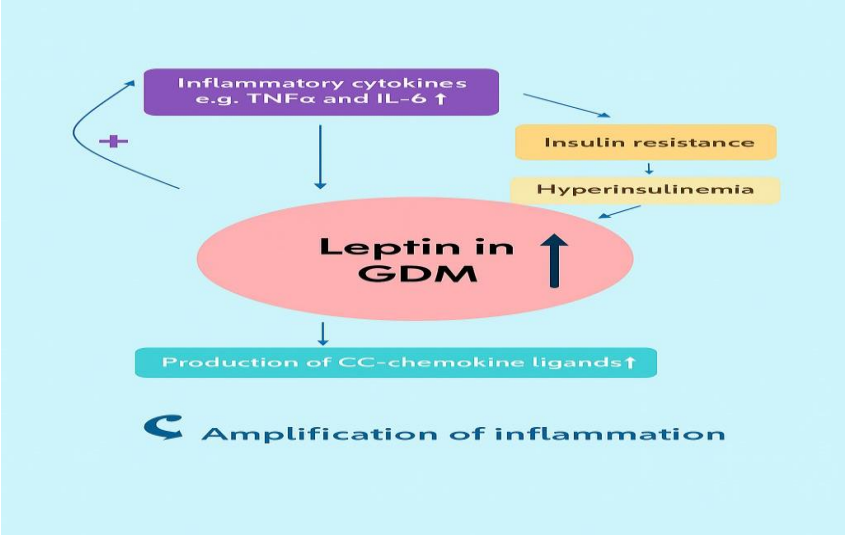


Fig 2- showing characteristics of Leptin in GDM.[12]

MATERIALS AND METHODS

The present study comprised a case-control study design involving 260 Pregnant individuals of which 160 were diagnosed with GDM. Diagnosis was established through clinical history, physical examination, and OGTT and HbA1c%. Cases were selected from the Obstetrics and Gynaecology dept of Janana Hospital, Ajmer. Concurrently, age and gender-matched controls (n=100) were selected from the Outpatient Department of the same institution. A comparative analysis of patient data was conducted against the 100 healthy controls. Patients with GDM who are taking Insulin, smokers, alcoholics, heart disease patients, Hypertensive, endocrine disorders, liver disease and Kidney disease were excluded. Overt Diabetes Type 1 and Type 2 DM cases are also excluded. Also those who didn't provide consent all were excluded from the study.

Procedure Blood samples were collected after administrating 50 gm anhydrous Glucose in plain vial or clot activator vial and one on EDTA Vail under aseptic conditions from all the study participants. All samples were centrifuged and analysed after 1 hour. Serum Glucose was estimated using GOD POD method using Beckman Coulter Biochemistry Analyzer (DXC700). HbA1C is estimated using HPLC method on D10 biochemical analyzer. Leptin was estimated using ELISA Method by Invitrogen kit. Overnight fasting sample was also taken for the estimation of Fasting Serum Insulin and Fasting Glucose on the same day before 1 hour PP Sample. HOMA-IR is calculated using fasting glucose and fasting insulin levels, and it provides a simple, cost-effective way to assess the degree of insulin resistance in a patient. The formula to calculate HOMA-IR is: -

$$\text{HOMA-IR} = \frac{\text{Fasting Insulin } (\mu U/mL) \times \text{Fasting Glucose } (mg/dL)}{405}$$

A value greater than 2.5 is commonly considered indicative of insulin resistance, though this threshold can vary based on population and study.

Data analysis

Collected data were entered into Microsoft Excel spreadsheet and then analysed by IBM SPSS (version 26). Data had been summarized as mean and standard deviation for numerical variables and count and percentages for categorical variables. A p value <0.05 was considered significant.

RESULTS

TABLE 1
AGE DISTRIBUTION

Age (in years)	Group I Without GDM (n = 100)		Group II With GDM (n = 160)		P value
	Number	Percent (%)	Number	Percent (%)	
≤ 30 years	66	66	80	50	p-value <0.0001(HS)
> 30 years	34	34	80	50	
Total	100	100	160	100	

The above table shows age distribution in our study. Out of 100 patients in Group I (without GDM) 66 patients (66%) were in the age group of ≤ 30 years and 34 patients were in the age group of >30 years. But in Group II (with GDM) out of 160 patients 80 patients were in the age group of ≤ 30 years and 80 patients were in the age group of > 30 years.

The Chi-square reveals a highly significant association between age and GDM status (p-value <0.0001). Women with GDM (Group II) were more likely to be above 30 years of age (50%) compared to women without GDM (Group I), who were more likely to be below 30 years of age (66%).

GRAPH 1 AGE DISTRIBUTION

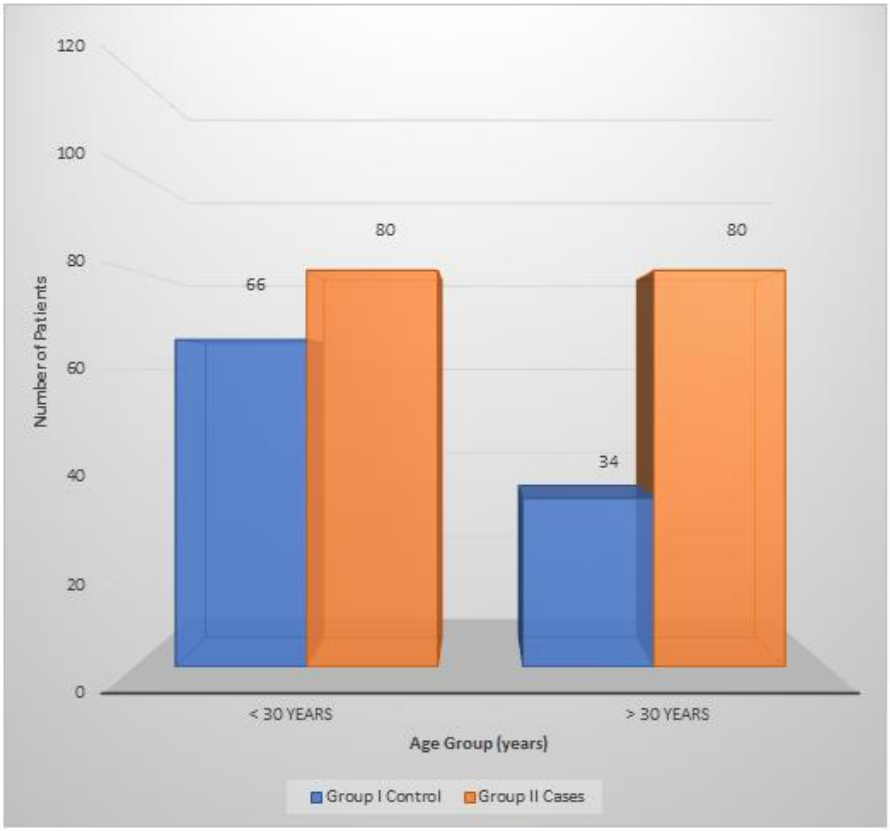


TABLE 2 COMPARISON OF GLYCEMIC MARKERS

Test	Group 1 Without GDM (n = 100)		Group 2 With GDM (n = 160)		P Value
	Mean	±SD	Mean	±SD	
Homeostatic model assessment for insulin resistance (HOMA-IR)	1.123	0.16	3.95	0.8	p<0.0001
Glycated Haemoglobin (HbA1c)	4.9	0.8	6.64	1.17	p<0.0001

The mean HOMA-IR values were significantly higher in Group II (With GDM) (3.95±0.8) compared to Group I (Without GDM) (1.123±0.16), indicating higher insulin resistance in women with GDM.
The mean HbA1c values were also significantly higher in Group II (With GDM) (6.64±1.17 %) compared to Group I (Without GDM) (4.9±0.8 %), indicating poorer glycemic control in women with GDM.

GRAPH 2 COMPARISON OF GLYCEMIC MARKERS

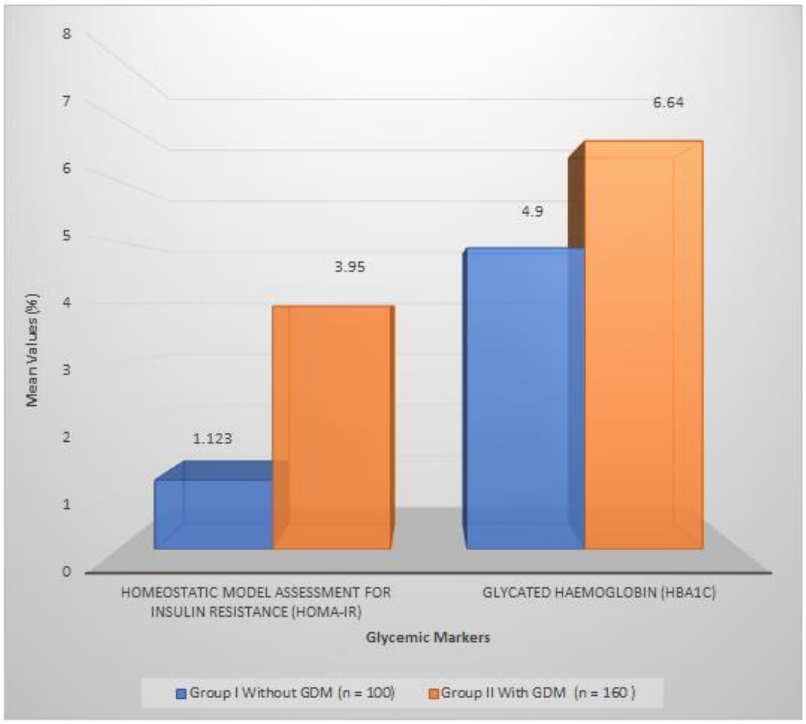


TABLE 3 COMPARISON OF LEPTIN IN GDM AND NON-GDM GROUPS

Parameters	Group I Without GDM (n = 100)		Group II With GDM(n = 160)		P Value
	Mean	±SD	Mean	±SD	
Serum Leptin (ng/ml)	70.59	6.06	87.91	4.32	P < 0.0001(HS)

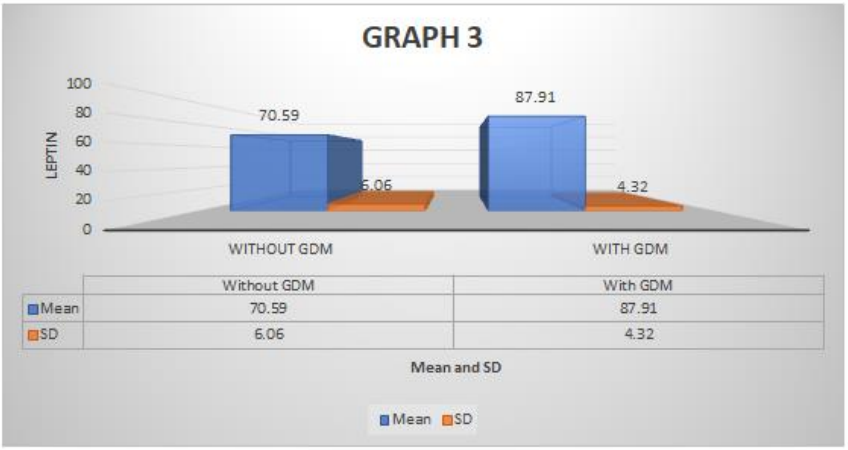


TABLE 4 CORRELATION OF SERUM LEPTIN LEVELS WITH GLYCEMIC MARKERS IN CONTROL AND CASE GROUP

Correlation of Serum Leptin with HOMA-IR and OGTT		Group I Without GDM (n = 100)	Group II With GDM (n = 160)
HOMA- IR	Pearson Correlation	0.164	0.0814

	P Value	**<0.0001**	**<0.0001**
OGTT	**Pearson Correlation**	**0.0291**	**-0.0115**
	P Value	**<0.0001**	**<0.0001**

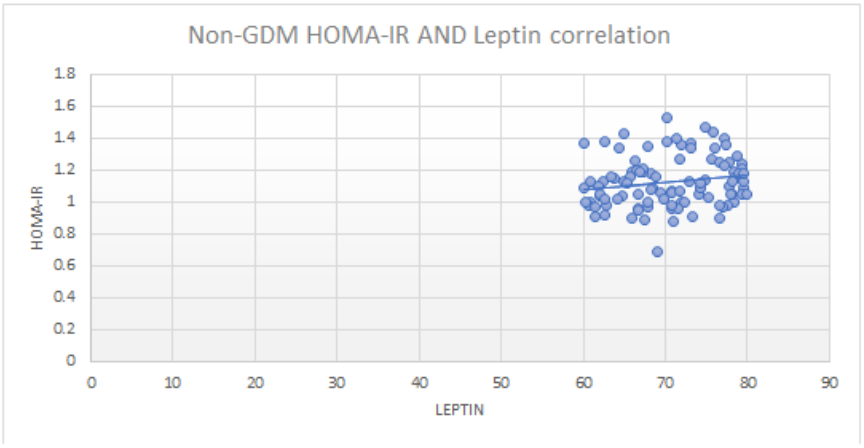
HOMA-IR Correlation:

- Group I (no GDM): There is a weak positive correlation (r = 0.164) between serum leptin and HOMA-IR, which is statistically significant ($p < 0.0001$). This suggests that as leptin increases, insulin resistance may also slightly increase in non-GDM women.
- Group II (with GDM): The correlation is even weaker (r = 0.0814), though still statistically significant. This weaker association might indicate altered leptin signaling or insulin resistance dynamics in GDM patients.

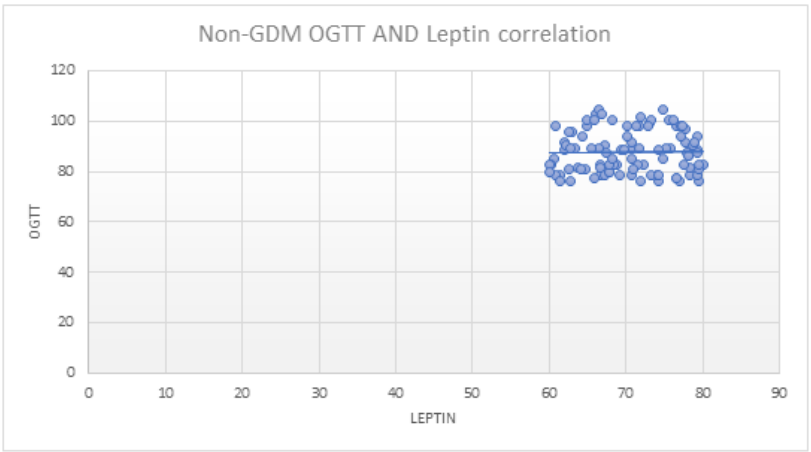
OGTT Correlation:

- Both groups show very weak or negligible correlations between leptin and OGTT results. In Group I, the correlation is slightly positive (r = 0.0291), while in Group II, it's slightly negative (r = -0.0115).

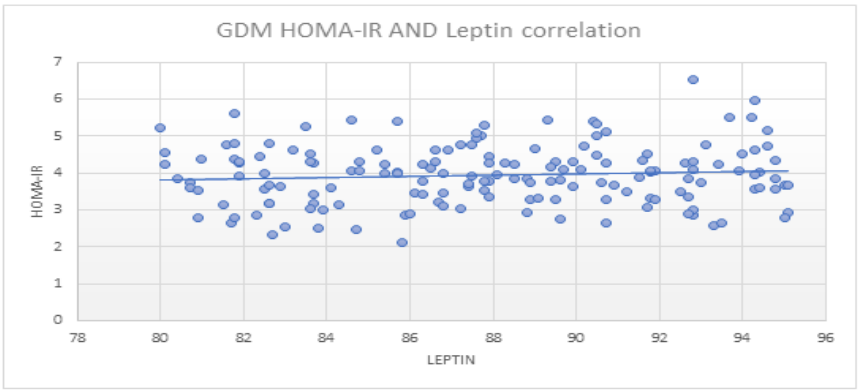
GRAPH 4



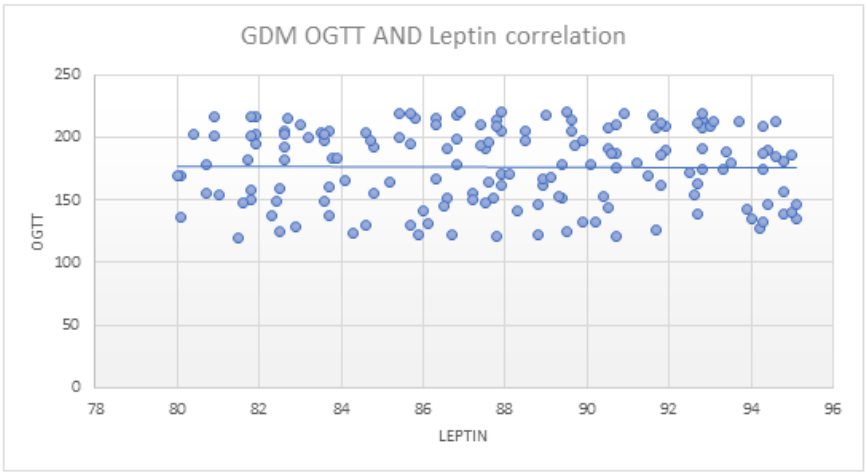
GRAPH 5



GRAPH 6



GRAPH 7



DISCUSSION

The present study aimed to investigate the role of leptin as a potential early biomarker for gestational diabetes mellitus (GDM), with particular focus on its correlation with glycaemic markers such as HbA1c and HOMA-IR. The results demonstrated a statistically significant elevation of serum leptin levels in women diagnosed with GDM compared to normoglycaemic pregnant controls. These findings align with existing literature suggesting that hyperleptinaemia, especially in early pregnancy, may be predictive of subsequent development of GDM.

The age distribution data revealed a strong association between advanced maternal age (>30 years) and GDM, consistent with previous reports indicating that maternal age is an established risk factor. While 66% of normoglycaemic women were under 30 years of age, 50% of GDM cases were over 30, a difference that was statistically significant ($p < 0.0001$). This supports the notion that advancing maternal age contributes to increased insulin resistance and metabolic stress, potentially exacerbating leptin dysregulation.

Biochemically, the GDM group showed significantly elevated HOMA-IR values (mean: 3.95 ± 0.8), suggesting marked insulin resistance. In parallel, the mean HbA1c values (6.64 ± 1.17%) were substantially higher in the GDM group compared to controls (4.9 ± 0.8%), reinforcing the clinical diagnosis of compromised glycaemic control.

The mean HOMA-IR values in the present study were 1.123±0.16 for women without GDM and 3.95±0.8 for women with GDM, with a significant p-value. These findings are consistent with Ademoghu E et al. (2015)[19] and Abd El Alla NK et al. (2022)[20], who also reported significant differences in HOMA-IR values between women with and without GDM.

Regarding HbA1c levels, in the present study it was found significant differences between women with and without GDM, with mean values of 4.9±0.8% and 6.64±1.17%, respectively. These findings are consistent with Ademoghu E et al. (2015)[19] and Hare KJ et al. (2014)[21], who also reported significant differences in HbA1c levels between women with and without GDM.

Importantly, leptin levels were significantly higher in GDM patients (87.91 ± 4.32 ng/ml) compared to controls (70.59 ± 6.06 ng/ml), with a p-value < 0.0001 indicating high statistical significance which is in accordance with the study by Latife Bozkurt et al. (2018).[22] He stated the leptin levels in GDM group were 93.4 ± 38.5 ng/ml and in Non-GDM were

78.0 ± 39.2 ng/ml with a p value <0.0001. This supports the hypothesis that leptin, possibly via its role in modulating insulin sensitivity and inflammatory pathways, is intricately involved in the pathophysiology of GDM.
The observed positive correlations between leptin and HOMA-IR (Group II: r = 0.0814) and OGTT (Group I: r = 0.0291) further strengthen the proposition of leptin's involvement in insulin resistance and glucose intolerance. Though the correlation coefficients appear modest, their statistical significance ($p < 0.0001$) implies that even subtle variations in leptin levels may have a meaningful impact in the context of gestational metabolic changes.
In the study conducted by Andrea Roxana Florian et al (2021)[23] elevated leptin levels were found associated with GDM. Maternal leptin levels were significantly higher in GDM patients ($p<0.00001$) in the study conducted by Jie xu et al (2014).[24] Yang Liu et al (2023)[25] implied in his research that Leptin may be a predictor of GDM. In the systemic review done by María del Mar Roca-Rodríguez et al (2022)[26] high levels of leptin were found correlated with GDM. Increased first trimester Leptin is associated with GDM ($p<0.0001$) was found in the study done by Ahmed Tizani Bawah et al (2019).[27] Higher levels of leptin showed positive correlation with GDM was reported by Seyedeh Neda Mousavi et al (2023)[28] and Konstanze Miehle et al (2012).[12]

CONCLUSION

This study underscores the significant elevation of serum leptin levels in women diagnosed with gestational diabetes mellitus (GDM) and highlights its potential utility as an early biomarker. The strong statistical association between hyperleptinaemia and key indicators of insulin resistance (HOMA-IR) and poor glycaemic control (HbA1c) supports leptin's role in the pathophysiology of GDM. These findings align with previous literature suggesting that elevated leptin, independent of maternal adiposity, may reflect early metabolic derangements preceding clinical onset of GDM. Incorporating leptin screening in early pregnancy could improve risk stratification, allowing for earlier intervention and improved maternal-foetal outcomes. Further longitudinal studies with larger cohorts are recommended to validate leptin's predictive capacity and explore its integration into routine antenatal screening protocols.

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