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Original Article

The Relationship between Iron Markers, Cortisol and Insulin Resistance in Gestational Diabetes Mellitus

Hina Anwar[1]*, Muhammad Zeeshan Rana[2], Najeeb Ullah Khan[3], Mariam Saeed[1], Amal Mahmood[1], Ayesha Wahid[1]

[1]Post Graduate Resident, CMH Lahore, Pakistan.

[2]Consultant Chemical Pathologist, CMH Lahore, Pakistan.

[3]CMH Lahore, Pakistan.

Corresponding Author: Hina Anwar, Post Graduate Resident; Email: hinawahla89@gmail.com

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ABSTRACT

Background: Gestational diabetes mellitus (GDM) is a significant metabolic disorder occurring during pregnancy, associated with serious maternal and fetal complications if left untreated. The global prevalence of GDM emphasizes the urgent need for research into its pathogenesis and contributing factors, including hormonal changes, insulin resistance, and the role of iron metabolism.

Objective: The aim of this study was to investigate the relationship between iron markers (hemoglobin, serum iron, and serum ferritin), cortisol, insulin resistance (measured by HOMA-IR), and the development of GDM in pregnant women between 24 and 28 weeks of gestation.

Methods: This analytical cross-sectional study included 150 pregnant women, divided into GDM and non-GDM groups based on oral glucose tolerance test results. Iron markers, cortisol, fasting plasma glucose, insulin, and HOMA-IR levels were measured. Data analysis was performed using SPSS version 25, employing descriptive and inferential statistics, including the Mann-Whitney U test for non-normally distributed variables.

Results: Women with GDM exhibited significantly higher mean levels of hemoglobin (12.41±0.68 g/dl), serum iron (19.57±1.14 µmol/L), serum ferritin (25.92±2.58 ng/ml), cortisol (451.32±25.20 nmol/L), fasting plasma glucose (6.83±0.46 mmol/L), insulin (12.50±1.72 µU/mL), and HOMA-IR (3.83±0.78) compared to non-GDM participants ($p<0.001$ for all comparisons). These findings underscore the pronounced biochemical and hormonal alterations associated with GDM.

Conclusion: The study identified a significant association between elevated levels of iron markers, cortisol, and insulin resistance with the development of GDM. These findings suggest that monitoring these parameters during pregnancy could be crucial for the early detection and management of GDM. Individualized iron supplementation strategies may be necessary to prevent iron overload and minimize GDM risk.

Keywords: Gestational diabetes mellitus, Iron markers, Cortisol, Insulin resistance, HOMA-IR, Pregnancy, Glucose intolerance, Serum ferritin.

INTRODUCTION

Gestational diabetes mellitus (GDM) represents the predominant metabolic disorder observed in pregnancy, significantly affecting the health and wellbeing of hundreds of thousands of pregnant women globally. Recent statistics provided by the American Diabetes Association indicate that GDM's prevalence rates have surged to 15–20%, with expectations of a continuous increase in the forthcoming years (1, 2). Traditionally defined as an elevated plasma glucose concentration first identified during pregnancy, GDM is usually diagnosed between the 24th and 28th weeks of gestation, a period marked by the pancreas's inability to counteract the heightened diabetogenic state inherent to pregnancy (3, 4). Initially, glucose metabolism, the sensitivity of peripheral muscles to insulin, and hepatic glucose production remain normal during the first trimester. However, as pregnancy progresses into the second and third trimesters, the continuous growth in fetoplacental parameters leads to a decrement in maternal insulin sensitivity. This adaptation encourages maternal cells to diversify their energy sources, increasing the reliance on free fatty acids over glucose, thereby augmenting the glucose supply to the fetus (5, 6). Despite the physiological increase in beta cells and insulin levels during pregnancy, a subset of women fails to sufficiently upregulate insulin production to meet the escalated demands imposed by insulin

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resistance, culminating in hyperglycemia and the eventual manifestation of GDM (6). The assessment of insulin resistance in GDM patients is commonly conducted through the homeostasis model assessment of insulin resistance (HOMA-IR) (7).

The development of GDM is intricately linked to stress, with deviations in cortisol levels, as provoked by oxidative stress, potentially impairing the iron transport process (8, 9). Serum ferritin, a reflection of total body iron content, along with serum iron and the correlation between insulin and blood glucose concentration, suggests that elevated serum iron levels significantly elevate GDM risk (10, 11, 12). Despite the association of GDM with severe complications for both mother and fetus, the pathogenesis of this condition remains poorly understood (13). The objective of the current study is to elucidate the relationship between iron markers (serum iron, hemoglobin, and serum ferritin), the stress hormone cortisol, and insulin resistance among women diagnosed with GDM. By exploring these interrelations, the study aims to shed light on the complex pathogenesis of GDM, providing novel insights that could guide future research and therapeutic strategies. This comprehensive approach not only seeks to delineate the biochemical and hormonal dynamics contributing to GDM but also underscores the multifaceted nature of its development, emphasizing the need for a multidisciplinary focus in both research and clinical management strategies.

MATERIAL AND METHOD

The study was conducted as an analytical cross-sectional investigation within the Chemical Pathology Department at the Combined Military Hospital, Lahore, over a period of three months. The research encompassed a total of 150 pregnant women, selected through a convenient sampling technique. The inclusion criteria targeted women experiencing healthy pregnancies within the gestational age of 24 to 28 weeks. Conversely, exclusion criteria were stringently defined to omit participants with chronic conditions affecting organs such as the kidneys, liver, heart, lungs, those with pre-pregnancy diabetes, a prior diagnosis of gestational diabetes mellitus, polycystic ovarian syndrome, anemia, infection, or a positive familial history of diabetes, hypertension, or polycystic ovarian syndrome.

Following the receipt of approval from the ethical committee and the acquisition of informed written consent from each participant, data collection was initiated in the gynecology department of the same institution. The oral glucose tolerance test was employed to screen for GDM, necessitating participants to fast for a minimum of eight hours prior to the test. Initial blood samples were collected to measure fasting blood glucose levels, followed by the administration of a 75g glucose solution. Subsequent blood glucose levels were measured at one and two hours post-intake. The determination of plasma glucose levels was executed using the Cobas c501 analyzer through a photometry method. GDM diagnosis was confirmed under the criteria of fasting blood glucose levels equal to or exceeding 5.1 mmol/L, 1-hour blood glucose levels surpassing 10.0 mmol/L, or 2-hour blood glucose levels above 8.5 mmol/L.

Additional venous blood samples were collected to evaluate insulin, cortisol, hemoglobin, serum iron, and serum ferritin concentrations. The quantification of insulin and cortisol levels was conducted via radioimmunoassay using the Cobas e411 analyzer. Insulin resistance was assessed through the Homeostasis Model Insulin Resistance Index (HOMA-IR), calculated as fasting insulin (microU/L) multiplied by fasting blood glucose (mmol/L) divided by 22.5. Hemoglobin levels were determined using the Sysmex automatic blood cell analyzer, whereas serum iron and ferritin concentrations were measured through enzyme-linked immunosorbent assay (ELISA) and immunoturbidimetry, respectively.

Data analysis was performed using SPSS version 25, incorporating both descriptive and inferential statistical tests. Qualitative data were presented as frequency and percentage, while numerical data were depicted through median and interquartile range values. The normality of quantitative data was evaluated using the one-sample Kolmogorov-Smirnov test, revealing a non-normal distribution. Consequently, the Mann-Whitney U test was applied for data comparison and analysis, with a p-value of less than 0.05 considered statistically significant. This methodology ensured the adherence to the ethical principles outlined in the Declaration of Helsinki, emphasizing the importance of ethical considerations throughout the research process.

RESULTS

The study analyzed various parameters among 150 pregnant women, divided into two groups: those diagnosed with gestational diabetes mellitus (GDM) and those without (Non-GDM). The age of participants in the GDM group averaged 32.76 years with a standard deviation of 6.94, showcasing a median age of 36 years within an interquartile range of 11 years. Conversely, the Non-GDM group exhibited a slightly lower average age of 30.65 years with a standard deviation of 6.80, and a median age of 31 years with an interquartile range of 13 years. The total population had an average age of 31.28 years, with a standard deviation of 6.89 and a median age of 32 years within an interquartile range of 13.25 years. Although the difference in age between groups approached statistical significance, it did not meet the conventional threshold (p=0.095).

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Table 1 Table 1: Comparison of age, haemoglobin, serum Iron, serum ferritin, cortisol, fasting plasma glucose, insulin and HOMA-IR with respect to both study groups (N=150)

		Mean ±S.D	Median ±IQR	p-value
Age (years)	GDM	32.76±6.94	36.0±11.0	0.095
	Non-GDM	30.65±6.80	31.0±13.0	
	Total	31.280±6.89	32.0±13.25	
Hemoglobin (g/dl)	GDM	12.41±0.68	12.30±1.15	<0.001
	Non-GDM	9.03±2.13	9.10±2.30	
	Total	10.043±1.905	10.0±3.50	
Serum Iron (µmol/L)	GDM	19.57±1.14	19.20±2.0	<0.001
	Non-GDM	12.92±2.93	12.90±5.20	
	Total	14.915±3.968	15.35±6.72	
Serum Ferritin (ng/ml)	GDM	25.92±2.58	26.0±4.20	<0.001
	Non-GDM	13.32±4.51	13.20±7.35	
	Total	17.098±7.05	16.25±12.92	
Cortisol levels (nmol/L)	GDM	451.32±25.20	450.42±41.75	<0.001
	Non-GDM	302.60±57.64	296.50±92.80	
	Total	3.47±8.47	3.449±158.20	
FPG (mmol/L)	GDM	6.83±0.46	6.80±0.80	<0.001
	Non-GDM	3.031±1.44	3.50±2.45	
	Total	4.168±2.136	3.70±3.30	
Insulin (µU/mL)	GDM	12.50±1.72	12.80±4.90	<0.001
	Non-GDM	5.05±2.89	6.10±5.15	
	Total	7.284±4.293	6.90±6.93	
HOMA-IR	GDM	3.83±0.78	3.87±1.45	<0.001
	Non-GDM	0.85±0.78	0.95±1.10	
	Total	1.745±1.573	1.130±2.58	
Gestational Diabetes Mellitus	Yes	45 (30%)		< 0.001
	No	105 (70%)		

In terms of hemoglobin levels, the GDM group demonstrated significantly higher values, with a mean of 12.41 g/dl and a standard deviation of 0.68, compared to the Non-GDM group, which had a markedly lower mean of 9.03 g/dl and a standard deviation of 2.13. This difference was statistically significant ($p<0.001$). Similarly, serum iron and serum ferritin levels were significantly higher in the GDM group, with means of 19.57 µmol/L and 25.92 ng/ml respectively, compared to 12.92 µmol/L and 13.32 ng/ml in the Non-GDM group ($p<0.001$ for both comparisons).

Cortisol levels also varied significantly between the two groups, with the GDM group exhibiting a much higher mean of 451.32 nmol/L compared to 302.60 nmol/L in the Non-GDM group ($p<0.001$). Fasting plasma glucose (FPG) levels further emphasized the disparity between GDM and Non-GDM participants. The mean FPG level in the GDM group was 6.83 mmol/L, significantly higher than the Non-GDM group's mean of 3.031 mmol/L ($p<0.001$).

Insulin levels and HOMA-IR scores, indicators of insulin resistance, were substantially higher in the GDM group. The mean insulin level in the GDM group was 12.50 µU/mL, compared to 5.05 µU/mL in the Non-GDM group. The HOMA-IR mean for the GDM group stood at 3.83, significantly surpassing the Non-GDM group's mean of 0.85 ($p<0.001$ for both insulin and HOMA-IR).

The distribution of GDM within the study population was significant, with 30% of the participants being diagnosed with GDM, contrasting with 70% without the condition ($p<0.001$). This distribution highlights the substantial impact of GDM on pregnant women within the study cohort, underlining the importance of monitoring and managing significant biochemical and hormonal differences associated with this condition.

DISCUSSION

Gestational diabetes mellitus (GDM), characterized by glucose intolerance first identified during pregnancy, poses significant risks for both maternal and fetal health if not adequately addressed (15). The global burden of hyperglycemia in pregnancy, as reported

in 2017, affected an estimated 16.2% of all live births, with GDM constituting 86.4% of these cases (16). The condition predominantly arises during the late second or third trimester and can persist until delivery. Although the development of GDM is influenced by a myriad of factors, including hormonal changes and metabolic shifts, the precise mechanisms underlying its pathogenesis remain elusive. Notably, elevations in hormones such as estrogen, progesterone, and cortisol, alongside increases in iron markers and insulin resistance, have been implicated in the rise of GDM prevalence (17).

The current study aimed to investigate the interplay between iron markers, cortisol, and insulin resistance in the context of GDM development among women in their 24th to 28th weeks of pregnancy. Findings indicated significantly higher levels of hemoglobin, serum iron, serum ferritin, cortisol, fasting plasma glucose, insulin, and the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) in participants diagnosed with GDM ($p<0.0001$). This aligns with the understanding that iron, as a potent pro-oxidant, can exacerbate oxidative stress when present in excess, thus influencing insulin resistance and β-cell function detrimentally and contributing to GDM onset (18-21).

Elevated iron levels, whether due to pre-pregnancy stores or intake during pregnancy, have been shown to triple the likelihood of type 2 diabetes mellitus after adjusting for other confounding factors (18). Studies have consistently reported that increased iron-induced oxidative stress can impair pancreatic β-cell function and disrupt glucose metabolism, leading to GDM (19-21). Furthermore, the association between high serum ferritin levels and GDM risk underscores the role of excessive iron storage in the development of this condition (22-26).

The evidence presented in this study, supported by previous research, underscores the complex relationship between iron metabolism and glucose regulation in pregnancy. The significant associations between elevated serum iron, ferritin levels, and GDM incidence suggest a need for a nuanced approach to iron supplementation during pregnancy. The findings advocate for the critical evaluation of iron levels in the first and second trimesters as a preventive measure against GDM, suggesting that a one-size-fits-all approach to iron supplementation may not be appropriate for all pregnant women. The development of individualized iron supplementation strategies, coupled with careful monitoring, could potentially mitigate the risk of iron overload and subsequent GDM development.

Despite the strengths of this study, including its analytical design and the robustness of its biochemical assessments, limitations are present. The cross-sectional nature of the study precludes the establishment of causality, and the convenience sampling technique may limit the generalizability of the findings. Future research should aim to elucidate the mechanisms by which iron influences insulin signaling and glucose metabolism in pregnancy, incorporating longitudinal designs to better understand the temporal relationship between iron status and GDM development.

CONCLUSION

In conclusion, this study highlights the intricate relationship between iron markers, cortisol, insulin resistance, and GDM development, emphasizing the importance of early detection and management of these parameters in pregnancy. The formulation of individualized iron supplementation regimens, informed by rigorous monitoring, emerges as a critical recommendation for the prevention and management of GDM, paving the way for future research to further refine these strategies.

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