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Original Research Article

Association of serum ferritin with gestational diabetes mellitus: a longitudinal study

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ABSTRACT

Background: Serum ferritin is an iron storage protein, also functions as an acute phase reactant and is elevated in inflammatory environments. Elevated serum ferritin is also associated with iron overload. Inflammation and iron overload are linked to occurrence of gestational diabetes mellitus (GDM). The purpose of this research was to determine whether serum Ferritin levels are associated with GDM.
Methods: A total of 150 non anemic females with singleton pregnancy were enrolled in the study. Serum ferritin was measured at 12-16 weeks of gestation. Oral glucose tolerance test OGTT was done at 24-28 weeks and repeated at 32-34 weeks. Patients were observed for development of GDM and association of serum ferritin and GDM was evaluated.
Results: Among the participants (mean age 25.46±4.0 years), 26.0% were diagnosed with GDM. Higher serum ferritin levels (61-90 ng/ml) showed the highest percentage (48.7%) compared to other groups. Significant differences across groups with a p value of less than 0.001 was noted establishing association of serum ferritin with GDM.
Conclusions: We can infer that higher serum ferritin is associated with GDM.

Keywords: Antenatal care, Gestational diabetes mellitus, Oral glucose tolerance test, Serum ferritin

INTRODUCTION

Ferritin, an essential protein for iron storage, plays a pivotal role in regulating iron metabolism in the human body. As a positive acute-phase reactant, ferritin levels are known to rise in response to various acute or chronic disease conditions. Functionally, ferritin serves as an iron-binding protein and is distributed across intracellular and extracellular compartments. Among these, extracellular ferritin is particularly relevant for assessing iron homeostasis and detecting disruptions in iron levels.[1]

Abnormalities in ferritin levels have been implicated in several pathological conditions, including inflammatory diseases, neurodegenerative disorders, and malignancies.[2] Elevated serum ferritin, which reflects these altered conditions, has also been associated with gestational diabetes mellitus (GDM).[3]

GDM is characterized by hyperglycemia, disturbances in fat, carbohydrate, and protein metabolism. These disruptions result from deficiencies in insulin action or secretion and are specifically noted during pregnancy.[4] The condition is further marked by an impaired ability of pancreatic β-cells to adapt to the increased metabolic demands of pregnancy. This maladaptation, which includes reduced β-cell hyperplasia and hyperactivity, creates a scenario in which the insulin demands exceed the available secretion, leading to the clinical manifestation of GDM.[5]

The prevalence of GDM is a growing public health concern, as demonstrated in a study conducted by Gopalakrishnan et al in Lucknow, Uttar Pradesh. Their research revealed that GDM affected 41.9% of the studied population, reflecting the significant burden this condition places on maternal health.[6]

One of the hallmarks of GDM is systemic inflammation. Being an acute-phase reactant, serum ferritin levels increase substantially in inflammatory conditions, making it a potential biomarker in GDM cases. In addition, iron overload- another factor commonly associated with elevated ferritin levels- has been proposed to contribute to insulin resistance at the cellular level.[7] This resistance arises due to iron-induced oxidative stress and subsequent apoptosis of pancreatic islet cells, ultimately leading to a decline in the pancreas's insulin secretion capacity. Additionally, an interesting observation from studies is that iron deficiency anemia appears to confer a decreased risk of developing GDM, suggesting a potential inverse relationship between iron deficiency and hyperglycemia in pregnancy.[8]

While there is growing evidence from numerous studies supporting the association between elevated serum ferritin levels and GDM, the current data remain insufficient to recommend serum ferritin as universally accessible screening tool for GDM.[7-10] Further investigations are necessary to establish its utility and reliability for clinical applications.

This research aimed to delve deeper into the relationship between serum ferritin levels and GDM, with the goal of evaluating its potential as an effective diagnostic biomarker.

METHODS

It was a prospective cohort study carried out at Hind Institute of Medical Sciences, Barabanki,

Study duration was 18 months, with 12 months for data collection and six months for data analysis from October 2023 to April 2024.

Inclusion criteria

Pregnant women with a singleton pregnancy at 12-16 weeks of gestation.

Exclusion criteria

Anemia (hemoglobin <11 gm/dl), pre-existing type 1 or type 2 diabetes, hematological disorders (e.g., sickle cell anemia, hemoglobinopathies, thalassemia), autoimmune disorders, hepatitis, fever, infections, or inflammatory conditions.

Data were collected from the ANC outpatient department, obstetric ward admissions, and consultation referrals from casualty and other departments. The target age group was 18 to 40 years.

Sample size

Sample size was calculated by using the formula:

$$n = Z_{\alpha}^{2} p(1-p)E^{2}$$

P = prevalence or proportion

Z_{α}^{2} = critical value of Z-score at α level of significance (at α = 5%, Z_{α} = 19.6)

E = permissible error (margin of error)

Prevalence of GDM (there is an established correlation between elevated serum ferritin and GDM in Lucknow =41.9 %.[3,8,10,11]

P= 41.9%= 0.419

E=10 %=0.10 (Absolute margin of error)

$n = (1.96)^2 \times 0.419\ (1-0.419)(0.1)^2 = 144.54$

n = 150 (rounded off to 150).

Procedure

prospective study was done on pregnant women with 12-16-week gestational age. These subjects were recruited from the obstetrics OPD of Hind Hospital Barabanki, UP between November 2022 and November 2023 based on inclusion and exclusion criteria. General information including maternal age, obstetric history, past medical histories, socioeconomic status and family history were obtained. Patients' height and weight was measured, and BMI was obtained by dividing per-pregnancy weight in kilograms by the square of height in meters. Routine ANC investigations were sent. At 12-16 weeks of pregnancy 5ml venous blood sample was taken for measurement of serum ferritin. Serum ferritin was measured by fully automated bidirectionally interfaced chemiluminescent immuno-assay.

Prenatal iron supplementation was continued by all the participants based on the national policy. Assessment of gestational diabetes was done by an oral glucose tolerance test between 24-28 weeks of pregnancy. Testing using 75 gm of oral glucose was done and blood sugar was measured after 2 hours after ingestion. 75 gm glucose was given orally after dissolving in approximately 300 ml of water irrespective of fasting or non-fasting state. The intake of the solution was completed within 5-10 minutes. A plasma standardized glucometer was used to evaluate blood sugar 2 hours after the oral glucose load. If vomiting occurred within 30 minutes of oral glucose intake, the test was repeated the next day. If vomiting occurs after 30 minutes, the test was continued. The threshold blood sugar

level of ≥140 mg/dl was taken as cut off for diagnosis of GDM.

Ethical approval

Ethical approval obtained from ethical committee at Hind Institute of Medical Sciences.

Statistical analysis

Descriptive statistics was performed using statistical package for social sciences (SPSS) software. The categorical variable will be expressed as 26.0 quantitative variables percentages (%) and variables as mean and standard deviation (SD). For paired comparisons, an independent t-test was used. The Chi-square test or Fischer's-exact test will be used for intergroup comparison of categorical variables. All analysis was two-tailed and p <0.05 was considered statistically significant. The frequency of distribution of adverse fetomaternal outcome across quartile of serum ferritin level was assessed for statistical significance by Chi- square test.

RESULTS

Demographic characteristics

The study included 150 patients, with the largest proportion in the age group ≤24 years, comprising 76 patients (50.7% of the total). The age group 25-28 years accounted for 24.0% (36 patients), while 22.0% (33 patients) were in the 29-32 years category. The smallest group was those aged ≥33 years, with only 5 patients (3.3%). The mean age of the patients was 25.46±4.0 years.

Table 1: Demographic profile of patients.

Category	Subcategory	Number of patients (n=150)	Percentage	Mean value
Age group (years)	≤24	76	50.7	25.46±4.0
	25-28	36	24.0	
	29-32	33	22.0	
	≥33	5	3.3	
BMI group (kg/m²)	<18.5	2	1.3	
	18.5-24.99	131	87.3	22.8±2.5
	>25	17	11.3	
Socioeconomic status (Kuppuswamy Scale)	Upper	9	6.0	
	Upper middle	75	50.0	
	Lower middle	50	33.3	
	Upper lower	15	10.0	
	Lower	1	0.7	
Obstetric score	Primigravida	73	48.7	
	Multigravida	77	51.3	

Table 2: Distribution profile of studied patients based on risk factor.

Risk factor	Number of patients (n=150)	Percentage
Family history of GDM	10	6.67
Family history of HTN	1	0.7
History of macrosomia	5	3.3
History of preterm delivery	4	2.7
History of HDP	4	2.7
History of GDM	1	0.7
No risk factor	128	85.33

Table 3: Distribution of studied patients based on serum ferritin.

Serum ferritin (ng/ml)	Number of patients (n=150)	Percentage	Mean serum ferritin (ng/ml)
<30	82	54.7	36.6±24.1
30-60	30	20.0	
61-90	32	21.3	
>90	6	4.0	

Among the patients, 87.3% (131 patients) had a BMI within the normal weight range (18.5-24.99 kg/m^2). Only 1.3% (2 patients) had a BMI below 18.5 kg/m^2, while 11.3% (17 patients) were classified as overweight or obese (BMI >25 kg/m^2). The mean BMI of the patients was 22.8±2.5 kg/m^2. The majority of patients, 50.0% (75 patients), were in the upper-middle class, followed by 33.3% (50 patients) in the lower-middle class. Patients from the upper class and lower-upper class each made up 6.0% (9 patients) and 10.0% (15 patients), respectively. Only 0.7% (1 patient) belonged to the lower socioeconomic class. In terms of obstetric history, 48.7% (73 patients) were primigravida, while 51.3% (77 patients) were multigravida.

Risk factors for GDM

The most common risk factor for GDM was a family history of GDM, which affected 6.67% of patients. Other risk factors, such as a family history of hypertension, macrosomia, preterm delivery, hypertensive disorders of pregnancy (HDP), and previous GDM, were less common, affecting between 0.7% and 3.3% of patients. Since some patients reported more than one risk factor, the raw count of reported risk factors exceeded the study population, requiring careful consideration of overlap in the analysis.

Hemoglobin levels and serum ferritin levels

The majority of patients had serum ferritin levels below 30 ng/ml (54.7%, 82 patients). 20.0% (30 patients) had ferritin levels between 30 and 60 ng/ml, and 21.3% (32 patients) had levels between 61 and 90 ng/ml. Only 4.0% (6 patients) had ferritin levels greater than 90 ng/ml. The mean serum ferritin level was 36.6±24.1 ng/ml. The analysis found a statistically significant association between BMI and serum ferritin levels ($p<0.05$).

GDM prevalence

In this study, 26.0% (39 patients) were diagnosed with GDM. Among the patients with serum ferritin levels below 30 ng/ml, only 10.3% (4 patients) had GDM. However, the prevalence of GDM increased significantly with rising ferritin levels. Specifically, 33.3% (13 patients) of those with ferritin levels between 30-60 ng/ml were diagnosed with GDM, demonstrating a moderate association between these ferritin levels and the incidence of GDM. The association became stronger in the 61-90 ng/ml group, where 48.7% (19 patients) had GDM, suggesting a stronger correlation between elevated ferritin levels and GDM, in the cohort with ferritin levels exceeding 90 ng/ml, only 7.7% (3 patients) were diagnosed with GDM.

Statistical significance of serum ferritin and GDM

The correlation between serum ferritin levels and GDM was found to be statistically significant with a p value <0.001, indicating a robust association unlikely to have occurred by chance.

Table 4: Association of serum ferritin and GDM.

Serum ferritin (ng/ml)	GDM	%
<30	4	10.3%
30-60	13	33.3%
61-90	19	48.7%
>90	3	7.7%
P value	<0.001	

DISCUSSION

This study was conducted at the department of obstetrics and gynecology at Hind Institute of Medical Sciences, involving the analysis of 150 patients to explore the relationship between elevated serum ferritin levels during early pregnancy and the risk of GDM. The following discussion integrates the study's findings, examines their clinical implications, and proposes future research directions.

Among the 150 patients enrolled in the study, the majority (50.7%, 76 patients) were aged below 24 years. The mean age of the participants was 25.46±4.0 years, consistent with studies like the one by Anushree et al, which reported mean ages of 27 years and 28 years for GDM and non-GDM groups, respectively.[12] Most patients belonged to the upper middle socioeconomic class (50.0%). The study also maintained a nearly equal distribution of primigravida (48.7%) and multigravida (51.3%) participants, which enhances the generalizability of the results across diverse patient populations (Table 1).

A total of 85.3% of the patients did not report any known risk factors. Among those who had risk factors**,** family history of GDM was the most frequent (6.0%), followed by macrosomia (2.7%) and preterm delivery (2.0%). These incidences are somewhat higher compared to national averages, where GDM is reported at 1.3% macrosomia at 3.8%, and preterm delivery at 12%, highlighting the variation and broad applicability of these findings (Table 2).[13-15]

The serum ferritin levels varied among the patients: 54.7% had ferritin levels below 30 ng/ml, 20.0% had levels ranging from 30-60 ng/ml, and 21.3% had levels between 61-90 ng/ml. A small fraction (4.0%) had ferritin levels exceeding 90 ng/ml. The mean serum ferritin level was 36.6 ± 24.1 ng/ml, aligning with the 37.55 ng/ml observed in a study by Ruchi et al.[16] The study also identified associations between low BMI (<18.5) and lower ferritin levels, while higher BMI (>25) was linked to higher ferritin levels, suggesting a relationship between body weight and serum ferritin levels. This is consistent with findings by Khan et al, who noted an association between increased BMI and serum ferritin, theorizing that this might be related to an inflammatory response (Table 3).[17]

The prevalence of GDM in the study was 26.0% (39 patients). Our analysis found a significant association between serum ferritin levels and the incidence of GDM. The highest proportion of GDM patients (48.7%) were in the 61-90 ng/ml ferritin group. A statistical significance was noted with a p value <0.001, indicating a strong correlation. This finding is consistent with research conducted by Abhijit et al in West Bengal, which linked elevated serum ferritin levels to an increased occurrence of GDM, regardless of other risk factors (Table 4).[18]

Additionally, a study from Andhra Pradesh found that a serum ferritin level >34.7 ng/ml between 24-28 weeks was associated with a 63% risk of developing GDM.[12] Despite only 6% of the study population reporting risk factors such as a family history of GDM, elevated serum ferritin levels were strongly correlated with the occurrence of GDM. In our study, multigravida patients exhibited a higher incidence of GDM (64.1%), and higher hemoglobin levels were also linked to GDM in 53.8% of cases.

The implications of our study extend to clinical practice, advocating for tailored monitoring of serum ferritin levels during prenatal care to identify at-risk pregnancies early. This proactive approach could potentially mitigate complications associated with both high and low ferritin levels, thereby optimizing maternal and neonatal health outcomes. Future research should aim to validate these findings in larger, multi centre cohorts and explore underlying mechanistic pathways linking serum ferritin to specific pregnancy complications study underscores the critical role of serum ferritin as a biomarker in predicting and managing maternal health outcomes. By elucidating the complex relationships between serum ferritin and pregnancy complications, this research contributes to advancing personalized care strategies aimed at improving maternal health.

Limitations of study were: small sample size- the study included only 150 participants, limiting generalizability. Single-center study- conducted at one hospital, which may not represent diverse populations. Potential confounders-factors like diet, inflammation markers, and genetics may influence outcomes.

CONCLUSION

The study found a significant association between elevated serum ferritin levels and the occurrence of GDM. Women with higher serum ferritin levels (61-90 ng/ml) had the highest prevalence of GDM, with statistical significance (p<0.001). These findings suggest that elevated ferritin, possibly due to inflammation or iron overload, may be a risk factor for GDM. While serum ferritin shows potential as a biomarker for identifying women at higher risk of GDM, further large-scale, multi-center studies are needed to establish its clinical utility and understand the underlying mechanisms. Early monitoring of ferritin levels during pregnancy could help in risk stratification and timely intervention to improve maternal and fetal outcomes.

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