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**Original Article**

# Association Between Maternal Serum Ferritin Concentration and Risk of Gestational Diabetes Mellitus and Adverse Fetal Outcomes

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## ABSTRACT

Gestational diabetes mellitus (GDM) is a common pregnancy-related metabolic disorder linked to serious maternal and fetal complications. Rising evidence indicates that elevated maternal iron stores, especially serum ferritin, may contribute to GDM and adverse neonatal outcomes, yet data from South Asia, particularly Pakistan, are limited. **Objectives:** To evaluate the association between maternal serum ferritin concentrations at different gestational ages and the risk of GDM and adverse fetal outcomes. **Methods:** A retrospective cohort study of 146 singleton pregnancies at Combined Military Hospital Multan measured ferritin at 16–18 and 28–32 weeks. Participants were categorized into ferritin quartiles, GDM was diagnosed via a 75-g Oral Glucose Tolerance Test (OGTT), and logistic regression assessed associations after adjusting for key maternal covariates. **Results:** Higher mid-gestation serum ferritin levels demonstrated a significant relationship with increased risk of GDM (adjusted OR for Q4 vs. Q1: 1.43; p=0.016). Elevated ferritin was also linked to macrosomia (adjusted odds ratio (AOR)=2.01; 95% confidence interval (CI): 1.09–3.67), large for gestational age (LGA) infants (AOR=2.01; 95% CI: 1.09–3.72), and increased neonatal head circumference (AOR=2.70; 95% CI: 1.53–4.77). Although higher ferritin levels were associated with a reduced risk of small for gestational age (SGA) (AOR=0.44; 95% CI: 0.17–1.17), this association was not statistically significant. In late pregnancy, ferritin showed an inverse relationship with macrosomia, suggesting time-dependent effects. **Conclusions:** Elevated maternal serum ferritin levels during mid-pregnancy are associated with an increased risk of GDM and fetal overgrowth outcomes.

## INTRODUCTION

Gestational diabetes mellitus (GDM) is diagnosed during the second or third trimester of pregnancy with 16.7% prevalence worldwide [1]. GDM is most prevalent in the Southeast Asian region, with the highest rate of 27% and live births with the disease 2 [2]. It is more prominent in low-middle-income countries (LMIC) where access to maternity care is often inadequate [3]. According to a Pakistani study, the prevalence rate of cases of GDM was 13.9% among pregnant women in South Asian region [4]. A recent meta-analysis of 27,034 pregnant women reported GDB prevalence of 16.7% in Pakistan, with provincial rates of 35.8% in Balochistan, 23.9% in Islamabad, 17.2% in Khyber Pakhtunkhwa, 13.2% in Sindh, and 11.4% in Punjab [5]. Iron is a trace element that serves the biological purpose of pregnant women and fetuses [6]. Incidentally, blood volume increases by approximately 50% and total red blood cell mass by about 25% during pregnancy, which leads to a tremendous iron deficiency [7, 8]. Therefore, expectant mothers are recommended to supplement their intake of iron during the gestation period to prevent iron

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deficiency anemia [9]. However, increased iron stores can as well increase susceptibility to some conditions, particularly glucose metabolism diseases [10]. The excessive iron stores result in increased reactive oxygen species and develop insulin resistance along with impairment of insulin production [11]. Hence, the balance of the risks and benefits of iron stores augmentation during pregnancy requires further studies [12]. Serum ferritin level (SFL) is a major indication of stores of iron and plays a crucial role in controlling the systemic iron balance. It is used frequently in clinical assessment to establish body iron stores [13]. Various prospective studies have been conducted to determine the correlation existing between maternal ferritin levels and the development of GDM, the findings of which have often been contradictory [14].

In spite of the literature, there is no uniform and region-specific evidence on the role of maternal serum ferritin levels in relation to the timing of onset of GDM and poor fetal outcomes in Pakistan, which demonstrates a knowledge gap. This poses a clinical dilemma on whether iron supplementation should be balanced with possible metabolic dangers in pregnancy. Therefore, this retrospective study aimed to evaluate the association between maternal serum ferritin concentrations at different gestational ages and the risk of GDM, as well as to find the linkage between SFL and adverse fetal outcomes in a Pakistani population.

## METHODS

A retrospective analysis was carried out involving 146 participants in the Combined Military Hospital, Multan, between March 2024 and March 2025. The sample size was calculated using the single population proportion formula; $n=Z^2 p(1- p)/d^2$, assuming a 20% prevalence (p) of GDM, 95% confidence level (Z=1.96), and 6.5% margin of error (d). Women at least 18 years old with confirmed singleton pregnancy and prenatal and delivery records were included. Exclusion criteria comprised multiple gestations, pre-existing diabetes, liver or renal disease (including nephritis), cardiovascular disorders, and acute respiratory infections during pregnancy. Maternal and neonatal baseline and follow-up data, including adverse effects, were collected using structured questionnaires and verified with hospital records (Feb–Mar 2025). Birth measurements were recorded, and serum ferritin and hemoglobin levels were analyzed. Ferritin change was calculated as the difference between 28-32 and 16-18 weeks' concentrations. GDM was identified using a 75-g oral glucose tolerance test performed during the 24–28 weeks of the gestation period. The SFL in both gestation periods was analyzed in the same hospital lab through standardized laboratory practices [13]. Blood glucose levels were assessed at fasting, one hour, and two hours following glucose consumption. The thalassemia history and hemoglobin levels were extracted from antenatal clinical records and laboratory reports. Neonatal anthropometric measurements and adverse outcomes were obtained from delivery records. Premature rupture of membranes (PROM), low birth weight (LBW), and stillbirth were recorded based on standard obstetric documentation. There were four groups based on serum ferritin quartiles. Medians and interquartile ranges described continuous data, while percentages summarized categorical variables. The chi-square and Kruskal–Wallis tests assessed group differences for categorical and continuous values, respectively. A subgroup analysis compared GDM and non-GDM participants, referencing the highest ferritin quartile. SPSS version 28.0 was used with significance set at $p < 0.050$ (two-tailed). Before enrolment, every participant gave written informed consent. The ethical approval was obtained from the institutional Ethical Committee of Combined Military Hospital, Multan (ERC No. 09/2024/13/Trg; dated 12th January 2024 ). Surgical procedures were carried out in compliance with the Declaration of Helsinki.

## RESULTS

The maternal age was similar in quartile ranges, with a median of 31.0-32.0 years. The median body mass index (BMI) was 20.5 kg/m$^2$, with 88.4% of women below 24.0 kg/m$^2$. Education was mainly college level and above (78.8%) and an equal distribution of quartiles (p=0.477). Smoking (0.7%) and alcohol use (0.7%) were not common. All pregnancies were natural (99.3%), with no substantial interquartile variation (p=0.939). Interestingly, there was a significant increase in fasting and 1–2-hour post-load glucose levels with the increase in serum ferritin concentrations ($p < 0.050$). GDM was most common in Q3 and Q4 (24% and 24% respectively) relative to 18-20% (p=0.008).

**Table 1:** Demographic and Baseline Characteristics of Participating Women

| Characteristics | Total (n=146) | Q1 <18.32 µg/L (n=37) | Q2 18.32–31.34 µg/L (n=36) | Q3 31.34–55.90 µg/L (n=37) | Q4 >55.90 µg/L (n=36) | p-value |
|---|---|---|---|---|---|---|
| Maternal Age (Years) | 30.0 (28.5, 34.0) | 30.0 (28.5, 33.0) | 33.0 (28.0, 34.0) | 33.0 (28.0, 33.0) | 32.0 (30.0, 33.0) | 0.254 |
| BMI (kg/m$^2$) | 20.5 (18.8, 22.3) | 20.4 (18.8, 22.1) | 20.4 (18.8, 22.2) | 20.6 (19.0, 22.3) | 20.6 (18.8, 22.5) | 0.634 |
| BMI < 24.0 (n, %) | 129 (88.4%) | 33 (89.2%) | 31 (86.1%) | 33 (89.2%) | 32 (88.9%) | 0.527 |

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| | | | | | | |
|---|---|---|---|---|---|---|
| BMI ≥24.0 (n, %) | 17 (11.6%) | 4 (10.8%) | 5 (13.9%) | 4 (10.8%) | 4 (11.1%) | |
| Education – College & above | 115 (78.8%) | 28 (75.7%) | 28 (77.8%) | 30 (81.1%) | 29 (80.6%) | 0.477 |
| Smoking status (n, %) | 1 (0.7%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (2.8%) | 0.237 |
| Alcohol consumption (n, %) | 1 (0.7%) | 1 (2.7%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0.018 |
| Conception – Natural (n, %) | 145 (99.3%) | 36 (97.3%) | 36 (100%) | 37 (100%) | 36 (100%) | 0.939 |
| Parity – Nulliparous (n, %) | 108 (74.0%) | 28 (75.7%) | 26 (72.2%) | 27 (73.0%) | 27 (75.0%) | 0.469 |
| Abortion History (n, %) | 47 (32.2%) | 11 (29.7%) | 12 (33.3%) | 12 (32.4%) | 12 (33.3%) | 0.673 |
| Thalassemia History (n, %) | 8 (5.5%) | 1 (4.0%) | 1 (3.0%) | 3 (9.0%) | 2 (8.0%) | 0.775 |
| Delivery Time Gestational Age (Weeks) | 38.5 (37.0, 41.0) | 38.5 (37.0, 41.0) | 38.5 (37.0, 41.0) | 38.5 (37.0, 41.0) | 38.5 (37.0, 41.0) | 0.336 |
| Hemoglobin (g/L) | 116.0 (114.0, 120.0) | 114.0 (112.0, 118.0) | 116.0 (114.0, 120.0) | 116.0 (114.0, 121.0) | 116.5 (114.0, 121.0) | <0.001 |

There was an increasing birth weight and head circumference with an increasing level of maternal serum ferritin. The highest quartile recorded the most prevalence of macrosomia (>4000 g) and large for gestational age (LGA) infants (16% and 20% each; p=0.020 each). However, small for gestational age (SGA) incidence decreased in quartiles (p=0.033), with an inverse relationship with ferritin levels. There was a substantial difference in large head circumference, Q1 to Q4 of 4% to 24% (p=0.002), but no significant difference in small head circumference. There was a statistical comparison in the rates of LBW, stillbirth, and PROM, though PROM and stillbirth rates were lower in the highest quartile.

**Table 2:** Newborn and Adverse Outcomes

| Newborn Characteristics | Total (n=146) | Q1 <18.32 µg/L (n=37) | Q2 18.32–31.34 µg/L (n=36) | Q3 31.34–55.90 µg/L (n=37) | Q4 >55.90 µg/L (n=36) | p-value |
|---|---|---|---|---|---|---|
| Male (n, %) | 82 (56.2%) | 14 (56%) | 18 (55%) | 19 (58%) | 14 (56%) | 0.855 |
| Female (n, %) | 64 (43.8%) | 11 (44%) | 15 (45%) | 14 (42%) | 11 (44%) | |
| Birth weight (g) | 3300 (3085, 3530) | 3280 (3050, 3515) | 3300 (3080, 3520) | 3320 (3100, 3550) | 3340 (3100, 3570) | 0.058 |
| Head circumference (cm) | 33.8 (33.0, 34.4) | 33.6 (33.0, 34.2) | 33.8 (33.0, 34.4) | 33.9 (33.0, 34.4) | 34.0 (33.0, 34.5) | 0.043 |
| Chest circumference (cm) | 32.8 (32.0, 33.6) | 32.8 (32.0, 33.5) | 32.7 (32.0, 33.5) | 32.8 (32.0, 33.6) | 32.9 (32.0, 33.7) | 0.201 |
| **Adverse effects in Mothers and Neonates** | | | | | | |
| PROM (n, %) | 19 (13.0%) | 3 (12%) | 4 (12%) | 4 (12%) | 4 (16%) | 0.020 |
| GDM (n, %) | 31 (21.2%) | 5 (20%) | 6 (18%) | 8 (24%) | 6 (24%) | 0.008 |
| Macrosomia (n, %) | 15 (10.3%) | 2 (8%) | 3 (9%) | 4 (12%) | 4 (16%) | 0.020 |
| LBW (n, %) | 6 (4.1%) | 1 (4%) | 1 (3%) | 2 (6%) | 1 (4%) | 0.568 |
| LGA (n, %) | 20 (13.7%) | 2 (8%) | 4 (12%) | 6 (18%) | 5 (20%) | 0.020 |
| SGA (n, %) | 10 (6.8%) | 2 (8%) | 2 (6%) | 3 (9%) | 1 (4%) | 0.033 |
| Stillbirth (n, %) | 2 (1.4%) | 0 (0%) | 0 (0%) | 1 (3%) | 1 (4%) | 0.178 |
| Big head circumference (n, %) | 21 (14.4%) | 1 (4%) | 3 (9%) | 5 (15%) | 6 (24%) | 0.002 |
| Small head circumference (n, %) | 6 (4.1%) | 1 (4%) | 2 (6%) | 2 (6%) | 1 (4%) | 0.842 |

During 16–18 weeks of gestation, as SFL increased across quartiles, the proportion of women diagnosed with GDM also rose from 6.3% in the lowest quartile to 8.8% in the highest quartile. The women in the highest serum ferritin quartile (>35.90 µg/L) had significantly higher odds of developing GDM compared to those in the lowest quartile (adjusted odds ratio (AOR): 1.43), with a clear positive trend across quartiles (p=0.016).

**Table 3:** Association Between Maternal Serum Ferritin and GDM

| Variables | Q1 <18.32 µg/L (n=37) | Q2 18.32–31.34 µg/L (n=36) | Q3 31.34–55.90 µg/L (n=37) | Q4 >55.90 µg/L (n=36) | p-value | Per-SD Increase |
|---|---|---|---|---|---|---|
| n (%) | 8 (6.3%) | 8 (6.3%) | 9 (6.9%) | 12 (8.8%) | – | – |
| OR (95% CI) | 1.00 (ref) | 1.12 (0.84–1.48) | 1.06 (0.80–1.40) | 1.46 (1.11–1.92) | 0.020 | 1.15 (1.05–1.27) |
| Multivariable Model | 1.00 (ref) | 1.05 (0.78–1.41) | 1.01 (0.76–1.35) | 1.43 (1.08–1.91) | 0.016 | 1.15 (1.05–1.26) |

Higher levels of serum ferritin in the mother at 16-18 weeks of gestation were strongly correlated with bad perinatal outcomes. Prevalence of PROM increased in the four quartiles up to 2.7% in the highest group (p=0.014). High levels of ferritin were also associated with increased risks of macrosomia and LGA, and both showed significant trends (p=0.020), with crude and adjusted odds ratios showing greater than twofold increases in the highest quartile. Conversely, SGA incidence decreased with a rise in ferritin, with an 0.7% in Q4 (p=0.033). Big head circumference escalated by quartiles (p=0.002), but little association was observed with small head circumference.

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**Table 4:** Association Between Maternal Serum Ferritin Levels and Adverse Effects in Mothers and Neonates (16-18 Weeks)

| Outcomes | Q1 <18.32 µg/L (n=37) | Q2 18.32–31.34 µg/L (n=36) | Q3 31.34–55.90 µg/L (n=37) | Q4 >55.90 µg/L (n=36) | p-value | Per-SD Increase |
|---|---|---|---|---|---|---|
| Premature Birth | 2 (1.4%) | 2 (1.4%) | 2 (1.4%) | 2 (1.4%) | | |
| OR (95% CI) | 1.00 (ref) | 1.01 (0.48–2.10) | 0.98 (0.47–2.07) | 1.21 (0.71–2.05) | 0.903 | 1.08 (0.91–1.27) |
| AOR (95% CI) | 1.00 (ref) | 1.01 (0.47–2.16) | 0.97 (0.46–2.06) | 1.20 (0.70–2.06) | | |
| PROM | 3 (2.1%) | 3 (2.1%) | 3 (2.1%) | 4 (2.7%) | | |
| OR (95% CI) | 1.00 (ref) | 1.13 (0.63–2.01) | 1.14 (0.63–2.06) | 1.81 (1.16–2.83) | 0.014 | 1.18 (1.03–1.34) |
| AOR (95% CI) | 1.00 (ref) | 1.15 (0.63–2.12) | 1.14 (0.63–2.08) | 1.82 (1.16–2.84) | | |
| Macrosomia | 2 (1.4%) | 2 (1.4%) | 3 (2.1%) | 4 (2.7%) | | |
| OR (95% CI) | 1.00 (ref) | 1.13 (0.56–2.30) | 1.69 (0.93–3.07) | 2.00 (1.10–3.64) | 0.020 | 1.19 (1.02–1.39) |
| AOR (95% CI) | 1.00 (ref) | 1.14 (0.56–2.32) | 1.66 (0.91–3.03) | 2.01 (1.09–3.67) | | |
| LGA | 3 (2.1%) | 4 (2.7%) | 5 (3.4%) | 5 (3.4%) | | |
| OR (95% CI) | 1.00 (ref) | 1.48 (0.77–2.82) | 2.11 (1.15–3.89) | 2.00 (1.09–3.69) | 0.020 | 1.15 (1.03–1.30) |
| AOR (95% CI) | 1.00 (ref) | 1.48 (0.77–2.83) | 2.12 (1.15–3.91) | 2.01 (1.09–3.72) | | |
| SGA | 2 (1.4%) | 2 (1.4%) | 1 (0.7%) | 1 (0.7%) | | |
| OR (95% CI) | 1.00 (ref) | 0.96 (0.45–2.06) | 0.47 (0.18–1.22) | 0.45 (0.17–1.18) | 0.033 | 0.86 (0.75–0.99) |
| AOR (95% CI) | 1.00 (ref) | 0.96 (0.44–2.07) | 0.47 (0.18–1.22) | 0.44 (0.17–1.17) | | |
| Big Head Circumference | 2 (1.4%) | 3 (2.1%) | 4 (2.7%) | 6 (4.1%) | | |
| OR (95% CI) | 1.00 (ref) | 1.28 (0.70–2.35) | 2.01 (1.13–3.58) | 2.71 (1.54–4.79) | 0.002 | 1.24 (1.08–1.42) |
| AOR (95% CI) | 1.00 (ref) | 1.28 (0.69–2.36) | 2.00 (1.12–3.58) | 2.70 (1.53–4.77) | | |
| Small Head Circumference | 1 (0.7%) | 2 (1.4%) | 2 (1.4%) | 1 (0.7%) | | |
| OR (95% CI) | 1.00 (ref) | 1.92 (0.82–4.47) | 1.92 (0.83–4.46) | 0.96 (0.35–2.62) | 0.654 | 0.91 (0.70–1.18) |
| AOR (95% CI) | 1.00 (ref) | 1.92 (0.82–4.48) | 1.92 (0.83–4.47) | 0.95 (0.34–2.61) | | |

## DISCUSSION

This research investigated the connections between SFL among pregnant women and the risks of GDM and neonatal adverse effects. The greater serum levels of ferritin at 16-18 weeks were correlated with much higher odds of GDM (adjusted OR of Q4 vs. Q1=1.43; p=0.016), macrosomia ( AOR=2.01; 95% CI: 1.093.67), LGA ( AOR=2.01; 95% CI: 1.093.72) and large head circumference ( AOR=These findings are similar to the Xie et al. who provided the results on a prospective study with 2,361 pregnant women in the multi-ethnic cohort in the United States. Their analysis estimated serum ferritin values at 10 weeks and 14-weeks of gestation and concluded that the highest quartile of women had a 2.43-fold higher risk of GDM (95% CI: 1.583.72) with no effect on BMI, age, race, dietary iron, and CRP [15]. Likewise, another research of 1,143 pregnant women in China, Fan *et al.* found that GDM was more prevalent in higher SFL (>70 ng/mL) during early pregnancy. Their adjusted OR associated with GDM in the highest quartile is 3.17 (95% CI: 1.74- 5.76), which is significantly higher than this study's findings. However, dose-response correlation was similar to this study (p=0.016) [16]. Differences in ferritin cut-offs, background iron deficiency, and population characteristics may account for this variation, highlighting the need for population-specific ferritin thresholds for GDM risk prediction [17]. Conversely, we do not find the same results as Gautam *et al.* who in their study assessed 570 pregnant women in Colombia and did not find significant correlations between the levels of ferritin in the first trimester and GDM in the post-partum period after controlling for the level of BMI and markers of inflammation. Their research stated an OR of 1.12 (95% CI: 0.761.66) of GDM among females with an SFL over 45 ng/mL [18]. This study also found that increased SFL at 16-18 weeks was linked with increased probabilities of macrosomia (more than 4000 g) and LGA infants. This agrees with the results of Zhang *et al.* who provided a prospective cohort study on 328 pregnant Turkish women. They reported that the ferritin level over 60 ng/mL showed a significant correlation with both the macrosomia (OR = 2.89; 95% CI: 1.23-6.77) and the high level of cord blood insulin, which indicated the mediation of a ferritin level by intrauterine hyperglycemia [19]. Furthermore, the negative correlation between high serum ferritin and SGA babies in our cohort (AOR in Q4=0.44; 95% CI: 0.171.17) is a reflection of the Li *et al.* study. They discovered that low periconceptual ferritin (<12 µg/L) was also significantly related to high risk of SGA (OR=1.96; 95% CI: 1.263.05) that was probably mediated by maternal anemia and placental oxygen delivery [20].

However, this study has some limitations, i.e., small sample size (n=146), retrospective design, and lack of inflammatory markers (e.g., CRP), which confound ferritin interpretation. So, a single-center military setting may limit generalizability. Future large-scale, multicenter

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prospective studies incorporating inflammatory and nutritional biomarkers are recommended to establish population-specific ferritin thresholds and clarify the causal relationship between maternal iron status, GDM, and adverse neonatal outcomes.

## CONCLUSIONS

This research found that elevated maternal SFL during the mid-gestational period was linked to a greater likelihood of developing GDM. Elevated ferritin was also significantly associated with macrosomia, large for gestational age infants, and increased neonatal head circumference; however, no statistically significant association was observed with small for gestational age.

## Authors' Contribution

Conceptualization: SM
Methodology: AI
Formal analysis: NN, LN, BG, JM
Writing and Drafting: NN
Review and Editing: NN, SM, AI, LN, BG, JM, SAA

All authors approved the final manuscript and take responsibility for the integrity of the work

## Conflicts of Interest

All the authors declare no conflict of interest.

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