International Journal of Reproduction, Contraception, Obstetrics and Gynecology
Ruchitha V et al. Int J Reprod Contracept Obstet Gynecol. 2026 Sep;15(9):3562-3568
www.ijrcog.org
pISSN 2320-1770 | eISSN 2320-1789

DOI: https://dx.doi.org/10.18203/2320-1770.ijrcog20263042

Original Research Article

Association of serum ferritin concentration in early pregnancy with the risk of subsequent development of gestational diabetes mellitus

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Received: 07 July 2026
Revised: 07 August 2026
Accepted: 13 August 2026

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ABSTRACT

Background: Gestational diabetes mellitus (GDM) is among the commonest medical complications of pregnancy and South Asian women are affected at lower body mass indices than Western populations. Serum ferritin reflects body iron stores and is also an acute-phase reactant; iron-catalysed oxidative stress may impair insulin action. We examined whether early-pregnancy ferritin predicts subsequent GDM.
Methods: In this prospective observational study, 111 antenatal women at 12–18 weeks were enrolled consecutively at a tertiary teaching hospital. Fasting serum ferritin was measured by chemiluminescent microparticle immunoassay. Women were followed to 24–28 weeks, when GDM was diagnosed by 75g oral glucose testing using American Diabetes Association criteria. Analysis used Mann–Whitney U and chi-square tests, Spearman correlation, multivariable logistic regression and receiver operating characteristic (ROC) analysis.
Results: GDM developed in 24/111 women (21.6%). Median ferritin was higher in the GDM group (55.35 vs 24.00 ng/mL; $p<0.0001$). GDM prevalence rose across ferritin quintiles from 8.7% to 77.3% ($p<0.0001$). Ferritin correlated with glucose challenge values ($\rho=0.576$; $p<0.0001$) and independently predicted GDM after adjustment for age, BMI, gravida and haemoglobin (adjusted odds ratio 2.41 per 10 ng/mL; 95% CI 1.68–3.44). Area under the ROC curve was 0.865; a cut-off of 39.9 ng/mL gave 79.2% sensitivity, 92.0% specificity and 94.1% negative predictive value.
Conclusions: Elevated early-pregnancy serum ferritin is independently and gradedly associated with subsequent GDM and discriminates well between affected and unaffected women. Ferritin is inexpensive and already widely measured antenatally and may permit risk stratification well before conventional screening; multicentre validation is required.

Keywords: Biomarker, Early pregnancy, Gestational diabetes mellitus, Iron metabolism, Insulin resistance, Serum ferritin

INTRODUCTION

GDM glucose intolerance of variable severity first recognised during pregnancy has become one of the commonest medical complications of pregnancy and its burden has risen steadily alongside increasing maternal age, higher pre-pregnancy adiposity and urbanised patterns of diet and activity.[1] South Asian women are affected disproportionately and characteristically develop GDM at lower body mass indices and at younger ages than their Western counterparts, which suggests that mechanisms beyond conventional adiposity-driven insulin resistance are operating in this population.[1,2] The clinical consequences are substantial and well-rehearsed: pre-eclampsia, polyhydramnios, operative delivery and a markedly increased lifetime risk of type 2 diabetes for the mother and macrosomia, shoulder dystocia, neonatal hypoglycaemia and long-term metabolic programming for the offspring.[18,19] What is less often emphasised is the timing problem. Universal screening identifies GDM at 24–28 weeks, by which point placental development is complete and fetal growth trajectories are already

established. The period in which lifestyle modification is likely to be most effective the first and early second trimester has by then largely passed. A biomarker measurable at booking would therefore alter not merely when the diagnosis is reached, but what can realistically be done about it.

Serum ferritin is an attractive candidate on both mechanistic and practical grounds. Iron in excess of requirement catalyses the generation of reactive oxygen species; the pancreatic β-cell, which has notably low antioxidant enzyme capacity, is unusually vulnerable to the resulting oxidative injury and iron also interferes with insulin signalling and glucose uptake in hepatocytes and skeletal muscle.[9,12] Pregnancy additionally involves a physiological suppression of hepcidin that increases intestinal iron absorption and placental transfer, so that iron handling in pregnancy is not simply a scaled-up version of the non-pregnant state.[20] Because ferritin is simultaneously an iron-storage protein and an acute-phase reactant, a raised concentration may equally signal subclinical inflammation, itself an established driver of insulin resistance an ambiguity that is central to interpreting the literature.

That literature is not uniform. The Camden study reported a two-fold increase in GDM risk in the highest ferritin quintile, but the association weakened once C-reactive protein and pre-pregnancy body mass index were taken into account, raising the possibility that ferritin marks inflammation rather than contributing causally.[3] Subsequent prospective cohorts in Iranian, Danish, Chinese and multiracial American populations have nonetheless described a consistent and graded relationship that survives adjustment for the main confounders and two quantitative syntheses have concluded that higher ferritin is associated with an increased risk of GDM across diverse settings.[4-11]

This question carries a particular weight in India. Universal antenatal iron and folic acid supplementation is national policy and is delivered, in practice, with little reference to baseline iron status, so that women who are already iron-replete routinely receive iron they do not require. Prospective and trial data on whether supplementation itself alters GDM risk remain inconsistent, but if iron excess contributes even partly to glucose intolerance, the implications for a programme of this scale are not trivial.[13,15,17] Indian studies addressing early-pregnancy ferritin are still few and fewer still combine quintile-based dose-response modelling with multivariable adjustment and a formal assessment of predictive performance.[16] The interest arose from routine clinical observation. Women who screened positive at 24–28 weeks in our antenatal clinic frequently had unremarkable booking profiles normal age, normal body mass index, no family history apart from a ferritin value at the upper end of the reference range, which in ordinary practice attracts no comment because it is not “abnormal”. We therefore conducted this prospective observational study to evaluate the association between serum ferritin measured at 12–18 weeks and the subsequent development of GDM, to characterise the shape of that relationship across the range of ferritin values and to determine whether ferritin performs well enough as a discriminatory test to be of practical use at booking.

METHODS

Study design and setting

This was a prospective, longitudinal observational study conducted in the Department of Obstetrics and Gynaecology at a tertiary care teaching hospital (Justice K. S. Hegde Charitable Hospital), Mangaluru, Karnataka, India, over a period of six months (May 2025 to October 2025).

Participants

All antenatal women attending the outpatient department for routine antenatal care between 12 and 18 weeks of gestation were screened for eligibility and enrolled consecutively after written informed consent, until the required sample size was achieved. Gestational age was established by last menstrual period and confirmed by a dating scan. Women with iron deficiency anaemia (haemoglobin <11 g/dL), pre-existing diabetes mellitus, medical disorders of pregnancy or autoimmune disease, haematological disorders, any local or systemic infection or body mass index >30 kg/m² were excluded. These exclusions were applied deliberately to reduce the two principal sources of confounding for ferritin, namely iron deficiency at one extreme and inflammatory or obesity-related elevation at the other.

Sample size

Based on a previously reported GDM incidence of approximately 18% among women with high ferritin versus 6% among those with normal ferritin, a minimum of 110 participants was required at 80% power and 5% significance. A total of 130 women were recruited to allow for attrition; 111 completed follow-up and were included in the final analysis.

Procedure

After an overnight fast, venous blood was drawn at enrolment for serum ferritin, measured by chemiluminescent microparticle immunoassay, together with fasting plasma glucose, haemoglobin and haematocrit. C-reactive protein was also measured to allow assessment of confounding by subclinical inflammation. Participants were followed through routine antenatal visits and underwent 75 g oral glucose testing at 24–28 weeks. GDM was diagnosed when the fasting value was ≥92 mg/dl, the one-hour value ≥180 mg/dl or the two-hour value ≥153 mg/dl, in accordance with American diabetes association criteria.[18,19]

Ethical considerations

The study was approved by the Institutional Ethics Committee, K. S. Hegde Medical Academy, prior to commencement. Written informed consent was obtained from every participant and confidentiality was maintained by coding all samples and records.

Statistical analysis

Data were entered in Microsoft Excel and analysed using IBM SPSS Statistics version 29.0. Distribution was assessed by the Kolmogorov–Smirnov test; continuous variables are presented as mean±standard deviation or median (interquartile range) accordingly and categorical variables as frequencies and percentages. Between-group comparisons used the independent t-test or Mann–Whitney U test and the chi-square test for categorical variables. The correlation between ferritin and glucose challenge values was assessed by Spearman's rho. Multivariable logistic regression adjusted for age, body mass index, gravida and haemoglobin, with ferritin modelled per 10 ng/mL increment. Receiver operating characteristic (ROC) curve analysis determined the optimal ferritin cut-off by the Youden index, with sensitivity, specificity, predictive values and overall accuracy. A two-sided p value <0.05 was considered statistically significant.

RESULTS

Of 111 women completing follow-up, 24 developed GDM at 24–28 weeks, an incidence of 21.6%. Mean age was 27.21±3.63 years and mean body mass index 23.51±2.65 kg/m². Serum ferritin was significantly higher in women who subsequently developed GDM than in those who did not (median 55.35 (IQR 39.90–65.62) versus 24.00 (16.20–31.20) ng/ml; p<0.0001), as were glucose challenge values (p<0.0001). Age, body mass index, gravida and haemoglobin did not differ significantly between the two groups (Table 1, Figure 1, Figure 2). The relationship was graded rather than threshold-like. GDM prevalence rose across ferritin quintiles from 8.7% in the lowest to 77.3% in the highest, with the increase concentrated in the top quintile (chi-square p<0.0001) (Table 2, Figure 3).

Serum ferritin showed a moderate positive correlation with glucose challenge values (Spearman's ρ=0.576; p<0.0001) (Figure 4). On multivariable logistic regression, ferritin remained an independent predictor of GDM after adjustment for age, body mass index, gravida and haemoglobin (adjusted odds ratio 2.41 per 10 ng/mL rise; 95% CI 1.68–3.44; p<0.0001), while none of the covariates was independently predictive. ROC analysis demonstrated good discrimination (area under the curve 0.865; 95% CI 0.750–0.960). At the Youden-optimal cut-off of 39.9 ng/mL, sensitivity was 79.2%, specificity 92.0%, positive predictive value 73.1%, negative predictive value 94.1% and overall accuracy 89.2% (Table 3, Figure 5). The asymmetry between positive and negative predictive value indicates that the test is most informative in excluding risk when ferritin is low.

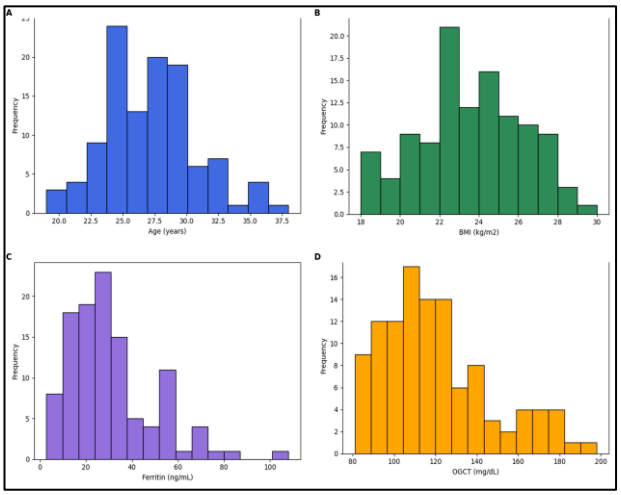

Figure 1 (A-D): Distribution of baseline variables in the study population (n=111). Maternal age; body mass index; early-pregnancy serum ferritin; oral glucose challenge test values at 24–28 weeks.

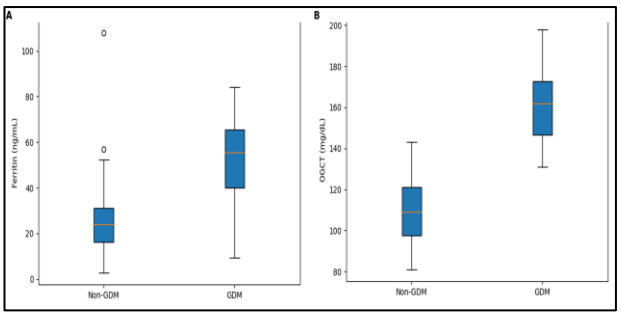

Figure 2 (A, B): Serum ferritin and glucose challenge values by GDM status. Early-pregnancy serum ferritin; oral glucose challenge test values. Both differed significantly between groups (Mann–Whitney U test, p<0.0001). Boxes show median and interquartile range; whiskers 1.5×IQR; circles denote outliers.

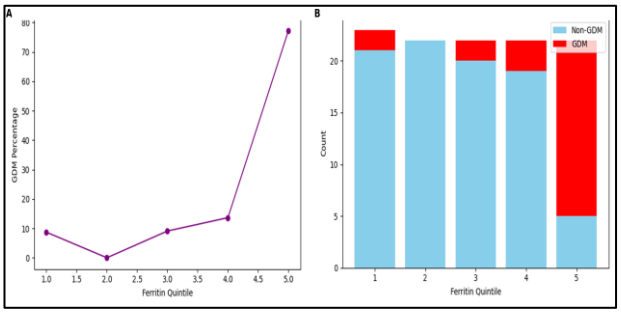

Figure 3 (A, B): Relationship between serum ferritin quintile and GDM. Proportion of women developing GDM in each ferritin quintile; absolute counts of GDM and non-GDM women per quintile. Chi-square p<0.0001.

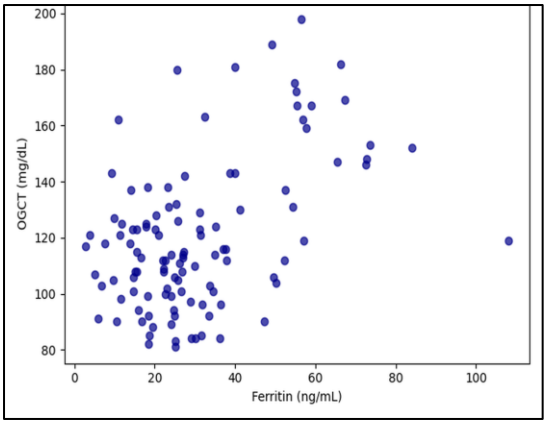

Figure 4: Scatter plot of early-pregnancy serum ferritin against oral glucose challenge test values. Spearman's ρ=0.576, p<0.0001.

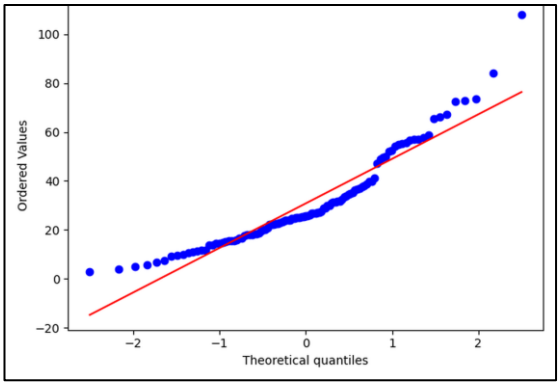

Figure 5: Receiver operating characteristic curve for serum ferritin in the prediction of GDM. Area under the curve 0.865 (95% CI 0.750–0.960); optimal cut-off 39.9 ng/ml (Youden index). The diagonal represents chance performance.

Table 1: Baseline characteristics of the study population overall and by GDM status (n=111).

Variables	Total (n=111)	Non-GDM (n=87)	GDM (n=24)	P value
Age (in years), mean±SD	27.21±3.63	27.20±3.61	27.25±3.80	0.9502
BMI (kg/m²), mean±SD	23.51±2.65	23.64±2.80	23.04±1.99	0.2451
Gravida, median (IQR)	3.00 (2.00–4.00)	3.00 (2.00–4.00)	3.00 (1.75–4.00)	0.7842
Haemoglobin (g/dl), median (IQR)	12.00 (11.45–12.80)	12.00 (11.35–12.85)	12.05 (11.65–12.43)	0.8915
Serum ferritin (ng/ml), median (IQR)	25.70 (18.05–37.75)	24.00 (16.20–31.20)	55.35 (39.90–65.62)	<0.0001
OGCT (mg/dl), median (IQR)	115.00 (101.00–131.50)	109.00 (97.50–121.00)	162.00 (146.75–172.75)	<0.0001
GDM, n (%)	24 (21.6)	—	—	—

Table 2: Distribution of GDM across serum ferritin quintiles.

Ferritin quintile	Range (ng/ml)	Total (N)	GDM, N (%)
1	2.8–15.5	23	2 (8.7)
2	15.5–23.5	22	0 (0.0)
3	23.5–30.0	22	2 (9.1)
4	30.0–47.2	22	3 (13.6)
5	47.2–108.0	22	17 (77.3)

Table 3: Independent association of serum ferritin with GDM and its predictive performance.

Panel A. multivariable logistic regression	Adjusted OR	95% CI	P value
Ferritin (per 10 ng/ml)	2.41	1.68–3.44	<0.0001
Age (in years)	0.95	0.81–1.11	0.5130
BMI (kg/m²)	0.96	0.77–1.20	0.7433
Gravida	1.17	0.70–1.95	0.5510
Haemoglobin (g/dl)	0.99	0.50–1.97	0.9877
Panel B. ROC analysis of serum ferritin	**Value**		
Area under the curve (95% CI)	0.865 (0.750–0.960)		
Optimal cut-off (Youden index)	39.9 ng/ml		
Sensitivity	79.2%		
Specificity	92.0%		
Positive predictive value	73.1%		
Negative predictive value	94.1%		
Overall accuracy	89.2%		

DISCUSSION

In this prospective study of 111 antenatal women, serum ferritin measured at 12–18 weeks was significantly and independently associated with the subsequent development of GDM, showed a graded relationship across quintiles and discriminated well between women who did and did not develop the condition (area under the curve 0.865).

The observed incidence of 21.6% is higher than that reported from most Western cohorts but is consistent with the pattern described in Asian populations, in whom GDM occurs at lower body mass indices and younger ages.[1,2] Notably, neither age nor body mass index differed between our groups and neither was independently predictive on regression a finding that would be surprising in a European cohort but is congruent with the South Asian phenotype, in which insulin resistance is not principally a function of measured adiposity. In such a population the conventional clinical risk-factor checklist performs poorly, which strengthens rather than weakens the case for a biochemical marker.

The directional finding agrees with earlier prospective work reporting higher early-pregnancy ferritin in women who later develop GDM and with meta-analytic syntheses across diverse populations.[3-9] The magnitude we observed is nonetheless larger than that in most published cohorts. Two features of the design plausibly account for this. First, ferritin was sampled in a narrow and early gestational window, before the physiological dilution and iron mobilisation of later pregnancy blur between-woman differences.

Second, exclusion of anaemic, obese and infected women removed much of the noise that ordinarily contaminates ferritin as a measure of iron stores, so that the concentration measured is closer to a true reflection of body iron than it would be in an unselected sample. The same design choices limit generalisability and we regard them as a trade of external for internal validity rather than as an unqualified strength.

The dose-response gradient across quintiles is informative in itself. Risk was flat across the lower four quintiles and rose steeply only in the highest, which argues against a smooth linear effect across the physiological range and in favour of a threshold above which iron burden begins to matter. This pattern is consistent with the mechanistic account: modest iron stores are physiologically necessary and it is the surplus available to catalyse Fenton chemistry, generate reactive oxygen species and injure the β-cell that carries metabolic cost.[9,12] It is also consistent with the ROC finding that the discriminatory cut-off, 39.9 ng/ml, sits comfortably within what most laboratories report as normal.

The principal alternative explanation is confounding by inflammation, since ferritin is an acute-phase reactant. This was precisely the difficulty encountered in the Camden study, where adjustment for C-reactive protein and pre-pregnancy body mass index attenuated the association.[3] Authors addressed it by excluding women with clinical infection, autoimmune disease and obesity at recruitment and by measuring C-reactive protein at enrolment.

The persistence of a strong independent association in this comparatively clean sample suggests that inflammation alone does not account for the finding, although residual confounding by subclinical inflammatory activity cannot be excluded and hepcidin, transferrin saturation and soluble transferrin receptor which would have allowed iron status and inflammation to be separated more convincingly were not measured.[7,20]

Clinical implications

Measurement of ferritin at booking may identify a high-risk group some ten to twelve weeks before conventional screening, at a stage when dietary and lifestyle intervention still has time to act. The practical value here is asymmetric: with a negative predictive value of 94.1%, a low ferritin at booking is genuinely reassuring, whereas a high value identifies a group warranting closer surveillance rather than a diagnosis. Positioned this way, ferritin is a triage tool and not a substitute for the 24–28 week test.

A second implication follows for iron supplementation policy. Universal antenatal iron and folic acid supplementation is given in India largely without reference to baseline iron status; if the association we observed is causal, iron-replete women may be receiving iron of no benefit to them at some metabolic cost. Trial evidence on this point remains genuinely inconclusive and we would not argue from an observational study for any change in supplementation practice only that the question deserves a properly powered randomised answer in an iron-replete Indian population.[13.15,17]

Strengths

The strengths of this study are its prospective design with exposure measured well before outcome, a narrow and clinically meaningful gestational window for sampling, quintile-based characterisation of the dose-response relationship, multivariable adjustment for the main clinical confounders and formal ROC-based evaluation rather than significance testing alone.

Limitations

The limitations are equally clear. The sample is moderate and single-centre and the 24 outcome events limit the number of covariates that can be responsibly entered into the regression model, so the confidence intervals should be read as wide. The restrictive exclusion criteria, while methodologically deliberate, mean the findings cannot be

extended to anaemic or obese women who together constitute a large proportion of the Indian antenatal population. Dietary and supplemental iron intake was not quantified, ferritin was measured once rather than serially and the cut-off of 39.9 ng/ml is derived from and optimised within this dataset and will almost certainly perform less well elsewhere. External validation in a larger multicentre cohort, ideally with hepcidin and soluble transferrin receptor alongside ferritin, is the necessary next step.

CONCLUSION

Elevated serum ferritin in early pregnancy (12–18 weeks) is significantly and independently associated with the subsequent development of gestational diabetes mellitus, with a graded relationship across quintiles and good discriminatory accuracy (area under the curve 0.865; optimal cut-off 39.9 ng/ml).

Ferritin is inexpensive, widely available and frequently already measured in early pregnancy and may serve as an early marker for risk-stratified antenatal care. Its clearest present value lies in its high negative predictive value; larger multicentre studies with external validation are required before any ferritin threshold is adopted for routine screening.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Ruchitha V, Rai S. Association of serum ferritin concentration in early pregnancy with the risk of subsequent development of gestational diabetes mellitus. Int J Reprod Contracept Obstet Gynecol 2026;15:3562-8.