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A prospective study on the role of serum ferritin in predicting preterm labour in anemic pregnant

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Abstract
Background: Preterm birth remains a major contributor to neonatal morbidity and mortality worldwide. Emerging evidence suggests that elevated maternal serum ferritin during pregnancy, reflecting inflammatory activation rather than iron sufficiency, may be associated with preterm delivery. This study aimed to evaluate the association between mid-pregnancy serum ferritin levels and subsequent preterm birth among anemic pregnant women.
Methods: A prospective observational study was conducted over one year at a tertiary-care teaching hospital in West Bengal, India. A total of 100 anemic pregnant women (hemoglobin <11 g/dL) with singleton pregnancies were enrolled between 20 and 28 weeks of gestation and followed until delivery. Serum ferritin was measured at enrollment. Preterm birth was defined as delivery before 37 completed weeks of gestation. Comparisons between term and preterm groups were performed using appropriate statistical tests, and the discriminatory performance of ferritin was evaluated using receiver operating characteristic (ROC) analysis.
Results: Preterm birth occurred in 25.0% (25/100) of participants (95% CI: 17.5%-34.3%). Median serum ferritin levels were significantly higher among women who delivered preterm (74.6 ng/mL, IQR 62.1-96.8) compared with those delivering at term (41.1 ng/mL, IQR 30.5-56.2; p <0.001). Using a ferritin cut-off of ≥70 ng/mL, preterm birth occurred in 53.6% of women compared with 13.9% among those with lower ferritin levels, corresponding to an unadjusted odds ratio of 7.15 (95% CI: 2.63-19.42). Serum ferritin demonstrated moderate discriminatory ability for predicting preterm birth, with an AUC of 0.76.
Conclusion: Among anemic pregnant women, elevated mid-pregnancy serum ferritin levels were strongly associated with an increased risk of preterm birth. These findings support the role of serum ferritin as a clinically relevant marker reflecting inflammatory processes linked to preterm delivery and suggest its potential utility in antenatal risk stratification in anemic populations.

Keywords: Serum ferritin, preterm birth, anemia in pregnancy, inflammation; biomarkers, roc analysis, India

Introduction
Preterm labor remains one of the leading causes of neonatal morbidity and mortality worldwide, with a disproportionate burden in low-and middle-income countries. In India, where maternal under nutrition and anemia are highly prevalent, identifying early and reliable predictors of preterm labor is of considerable clinical importance. Among the various biological factors implicated, maternal iron status and particularly serum ferritin has received sustained attention as a potential link between anemia, inflammation, and adverse pregnancy outcomes.
Anemia during pregnancy is a well-established public health problem and has been consistently associated with poor obstetric outcomes, including preterm birth and low birth weight. Scholl and Reilly highlighted that iron deficiency and anemia adversely affect pregnancy outcomes through impaired oxygen delivery and altered maternal-fetal physiology, while also interacting with inflammatory pathways that influence the timing of parturition [2]. Indian data further support this association; Kumari *et al*., in a large study from Jharkhand, demonstrated that moderate and severe maternal anemia were significantly associated with increased risks of preterm delivery and low birth weight, emphasizing the relevance of anemia-related pathways in Indian populations [6].
Serum ferritin, traditionally used as a marker of iron stores, occupies a unique position in pregnancy because it also functions as an acute-phase reactant. This dual role complicates interpretation but also provides biological plausibility for its association with preterm labor. Osterholm and Georgieff described how chronic inflammation alters iron metabolism, leading to

elevated ferritin levels independent of iron stores, reflecting inflammatory activation rather than nutritional adequacy [3]. In pregnancy, such inflammatory processes are increasingly recognized as central to the pathophysiology of spontaneous preterm labor.

Several studies have specifically examined serum ferritin as a predictor of preterm labor. Tamura *et al*. reported that elevated mid-pregnancy serum ferritin levels were associated with an increased risk of early spontaneous preterm delivery, suggesting that ferritin may act as a marker of subclinical inflammation preceding labor onset [5]. Similarly, Saha *et al*. observed significantly higher serum ferritin levels among women who developed preterm labor compared to those delivering at term, supporting its potential role as a predictive biomarker [1]. These findings suggest that ferritin elevation in pregnancy may reflect inflammatory or infectious processes that trigger premature activation of labor pathways.

More recent work continues to reinforce this concept. Mosa demonstrated that acute-phase reactants, including ferritin, were significantly higher in women with preterm delivery, further supporting the hypothesis that systemic inflammation rather than iron sufficiency alone plays a critical role in preterm labor [4]. Collectively, these studies indicate that serum ferritin may serve as an accessible and biologically meaningful marker linking anemia, inflammation, and preterm birth risk.

Despite this evidence, data from prospective studies focusing specifically on anemic pregnant women in Indian tertiary-care settings remain limited. Given the high prevalence of anemia and the substantial burden of preterm birth in India, evaluating serum ferritin within this high-risk group may help refine risk stratification and guide closer surveillance. Therefore, the present prospective study was undertaken to assess the role of serum ferritin measured during mid-pregnancy in predicting preterm labor among anemic pregnant women attending a tertiary-care hospital in West Bengal.

Objectives

- To estimate the incidence of preterm labor/preterm birth (<37 completed weeks) among anemic pregnant women enrolled at 20-28 weeks and followed up to delivery.
- To compare mid-pregnancy serum ferritin levels (20-28 weeks) between women who deliver preterm and those who deliver at term.
- To determine whether serum ferritin can serve as a clinically useful predictor of preterm birth, including identifying an optimal ferritin cut-off for risk stratification (ROC-based).

Materials and Methods

Study design, setting, and period

A hospital-based prospective observational study was conducted in the Department of Obstetrics and Gynaecology, Gouri Devi Institute of Medical Sciences and Hospital, Durgapur, West Bengal, over a period of one year. Anemic pregnant women were enrolled during mid-pregnancy and followed prospectively until delivery to assess the occurrence of preterm birth.

Study population and sampling

A total of 100 anemic pregnant women attending antenatal care were recruited using consecutive sampling during the study period.

Inclusion criteria

- Pregnant women aged ≥18 years
- Singleton pregnancy
- Gestational age between 20 and 28 weeks at enrollment
- Anemia in pregnancy, defined as hemoglobin <11 g/dL
- Willingness to participate and comply with follow-up until delivery

Exclusion criteria

- Multiple pregnancy
- Known major fetal anomaly at enrollment
- Known hemoglobinopathies or chronic hematologic disorders
- Acute febrile illness, clinically apparent infection, or known chronic inflammatory/autoimmune disease at the time of sampling
- Chronic liver disease, chronic kidney disease, malignancy, or other systemic illness affecting ferritin levels
- Inability to complete follow-up or refusal to provide informed consent

Data collection and study procedures

At enrollment, demographic and obstetric details were recorded using a structured proforma. Clinical examination included measurement of height, weight, and blood pressure. Laboratory evaluation included measurement of hemoglobin and serum ferritin from venous blood collected at enrollment (20-28 weeks gestation). Participants received routine antenatal care and anemia management as per institutional protocols and were followed until delivery.

Outcome measure

The primary outcome was preterm birth, defined as delivery before 37 completed weeks of gestation, as documented in hospital delivery records.

Statistical analysis

Data were entered in a spreadsheet and analyzed using standard statistical software. Categorical variables are presented as frequency and percentage. Continuous variables are summarized as mean (±SD) or median (IQR) based on distribution; serum ferritin was summarized using median (IQR). The incidence of preterm birth was calculated as a proportion with a 95% confidence interval (CI). Serum ferritin levels were compared between preterm and term delivery groups using the Mann-Whitney U test.

Receiver operating characteristic (ROC) analysis was performed to assess the ability of serum ferritin to discriminate between preterm and term deliveries, and the area under the curve (AUC) with corresponding sensitivity and specificity was reported. Logistic regression was used to estimate odds ratios (OR) with 95% CI for the association between serum ferritin and preterm birth. To minimize overfitting, the multivariable model included a limited set of clinically relevant covariates. A p-value < 0.05 was considered statistically significant.

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Ethical considerations

The study was approved by the Institutional Ethics Committee of Gouri Devi Institute of Medical Sciences and Hospital. Written informed consent was obtained from all participants, and confidentiality was maintained throughout the study.

Results

Participant enrollment and baseline profile

During the one-year study period, 100 anemic pregnant women

(Hb <11 g/dL) with singleton pregnancies were enrolled between 20 and 28 weeks' gestation and followed prospectively until delivery. Complete follow-up data were available for all participants, and delivery outcomes were included in the final analysis.

Overall, 75 women (75.0%) delivered at term (≥37 completed weeks), and 25 women (25.0%) delivered preterm (<37 weeks). Baseline characteristics stratified by delivery outcome are presented in Table 1.

Maternal age differed between the two groups. Women who delivered preterm had a higher mean age (27.4±5.0 years) compared with those who delivered at term (24.7±3.7 years), and this difference was statistically significant (p = 0.020, Table 1). Gestational age at enrollment was comparable across groups (median approximately 24-25 weeks, p = 0.692) with enrollment distributed across the 20-28 week window, minimizing bias from differing timing of ferritin measurement. Parity distribution was also similar between term and preterm groups (median 1, p = 0.728).

A prior history of preterm birth was uncommon in the cohort and did not significantly differ by outcome. Specifically, among term deliveries, 6/75 (8.0%) reported prior preterm birth, compared with 2/25 (8.0%) among preterm deliveries (p = 1.000, Table 1).

With respect to anemia severity, most women had mild to moderate anemia, with a smaller subset having severe anemia at enrollment. The distribution of anemia severity did not significantly differ between term and preterm delivery groups (overall p = 0.595, Table 1). Mean hemoglobin was 9.1±1.2 g/dL in term deliveries and 8.7±1.2 g/dL in preterm deliveries; this difference did not reach statistical significance (p = 0.207).

Table 1: Baseline characteristics of anemic pregnant women by delivery outcome (N=100)

Characteristic	Term (n=75)	Preterm <37w (n=25)	p value
Age (years), mean ± SD	25.7±3.8	24.0±2.8	0.025
Gestational age at enrollment (weeks), median (IQR)	24 (22-27)	24 (23-26)	0.872
Parity, median (IQR)	1 (0-2)	1 (0-2)	0.214
Prior preterm birth, n (%)	9 (12.0)	3 (12.0)	1.000
Anemia severity, n (%)			0.846
— Mild	36 (48.0)	13 (52.0)	
— Moderate	30 (40.0)	10 (40.0)	
— Severe	9 (12.0)	2 (8.0)	
Hemoglobin (g/dL), mean ± SD	8.7±1.4	8.8±1.4	0.625
Serum ferritin (ng/mL), median (IQR)	41.1 (30.5-56.2)	74.6 (62.1-96.8)	<0.001

Incidence of preterm birth

The incidence of preterm birth (<37 weeks) in this cohort of anemic pregnant women was 25.0% (25/100), with a 95% confidence interval (Wilson) of 17.5% to 34.3%. Term delivery occurred in 75.0% (75/100) of participants.

Serum ferritin distribution and comparison by delivery outcome

Serum ferritin measured at enrollment showed a clear difference between women who delivered preterm and those who delivered at term (Table 1; Figure 1). Ferritin values were right-skewed in both groups; therefore, ferritin is presented as median (IQR).

Women who delivered preterm had a median ferritin of 74.6 ng/mL (IQR 62.1-96.8), whereas women who delivered at term had a median ferritin of 41.1 ng/mL (IQR 30.5-56.2). The difference in ferritin distributions between groups was statistically significant (Mann-Whitney U test, $p<0.001$). The separation in ferritin distributions is visually evident in Figure 1, where the preterm group shows an upward shift in median and interquartile range compared with the term group.

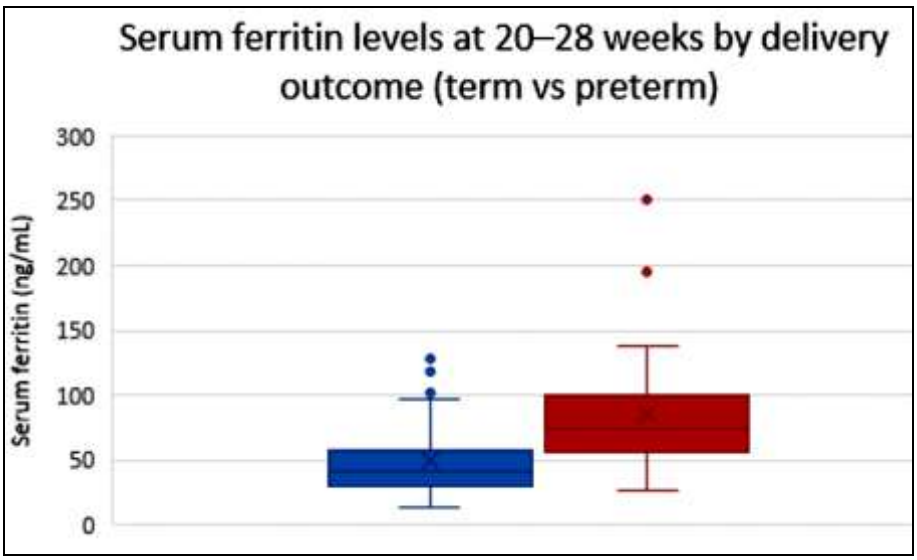

Fig 1: Serum ferritin (ng/mL) measured at enrollment (20-28 weeks) is shown for term and preterm deliveries. Boxes represent the interquartile range with the median line; whiskers represent 1.5×IQR; points denote outliers.

Ferritin cut-off analysis and stratified preterm risk

For clinical interpretability, ferritin was categorized using a pragmatic threshold of ≥70 ng/mL (Table 2). Using this cut-off, 28 women (28.0%) had ferritin ≥70 ng/mL and 72 women

(72.0%) had ferritin <70 ng/mL.

Preterm birth occurred in 15/28 (53.6%) women with ferritin ≥70 ng/mL, compared with 10/72 (13.9%) women with ferritin <70 ng/mL (Table 2). This corresponded to an unadjusted odds ratio of 7.15 (95% CI 2.63-19.42), and the association was statistically significant (Fisher's exact $p<0.001$). The absolute risk difference between groups was 39.7 percentage points (53.6% vs 13.9%), indicating a clinically meaningful stratification of preterm birth risk by ferritin category within this cohort.

Table 2: Preterm birth by serum ferritin category at enrollment (cut-off: 70 ng/mL) (N=100)

Serum ferritin category	Term (≥37w) n (%)	Preterm (<37w) n (%)	Total (n)	Unadjusted OR (95% CI)	p value
<70 ng/m L	62 (82.7)	10 (40.0)	72	Reference	
≥70 ng/m L	13 (17.3)	15 (60.0)	28	7.15 (2.63-19.42)	<0.001

Percentages in the Term column are column percentages (out of n=75 term deliveries), and percentages in the Preterm column are column percentages (out of n=25 preterm deliveries). Odds ratio calculated from the 2×2 table; p-value from Fisher's exact test.

Discriminatory ability of serum ferritin for identifying preterm birth

ROC curve analysis was used to evaluate the ability of ferritin to discriminate between women who subsequently delivered preterm versus term (Figure 2). Serum ferritin demonstrated moderate discriminatory performance, with an AUC of 0.76. The ROC curve showed improved sensitivity at higher ferritin thresholds, consistent with the observed higher ferritin distribution among preterm deliveries. The ROC results support ferritin as a clinically informative marker for risk stratification in this population, as reflected by an AUC in the mid-0.7 range (Figure 2).

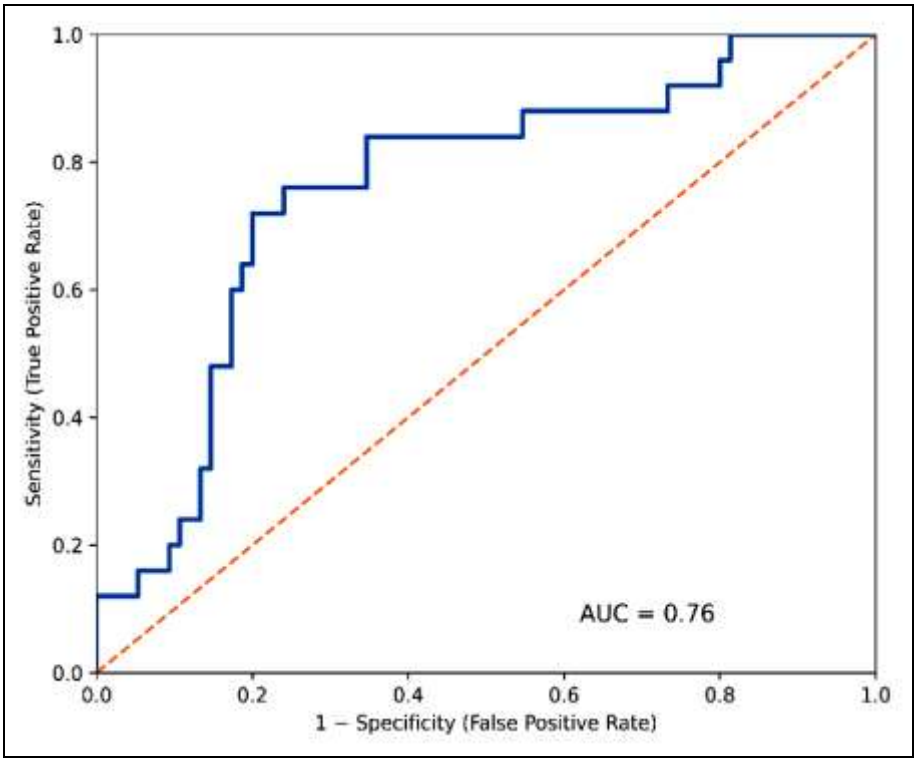

Fig 2: Receiver operating characteristic (ROC) curve for serum ferritin predicting preterm birth.

The ROC curve depicts the ability of mid-pregnancy serum ferritin (measured at 20-28 weeks) to discriminate between preterm (<37 weeks) and term deliveries among anemic pregnant women. The area under the curve (AUC) was **0.76**, indicating moderate discriminatory performance. The dashed diagonal line represents no discrimination (AUC = 0.5).

Overall, serum ferritin levels measured during mid-pregnancy were consistently higher among women who subsequently delivered preterm, with clear separation from term deliveries across descriptive, categorical, and ROC-based analyses. The incidence of preterm birth was substantial in this anemic cohort, and elevated ferritin (≥70 ng/mL) identified a subgroup with markedly higher preterm risk. Collectively, these findings demonstrate a reproducible association between higher mid-pregnancy serum ferritin levels and preterm birth in this study population.

Discussion

In this prospective study of anemic pregnant women, serum ferritin measured during mid-pregnancy (20-28 weeks) showed a clear and consistent association with subsequent preterm birth. Women who delivered preterm had substantially higher median ferritin levels (74.6 ng/mL) compared with those delivering at term (41.1 ng/mL), and a ferritin threshold of ≥70 ng/mL identified a subgroup with a markedly higher preterm birth rate (53.6% vs 13.9%). These findings align with and extend prior evidence suggesting that elevated ferritin in pregnancy reflects inflammatory activation rather than iron sufficiency.

Early work by Xiao *et al.* (2002) demonstrated that second-trimester ferritin elevation was only weakly associated with overall preterm delivery (OR 1.3, 95% CI 0.8-2.1) when comparing extreme quartiles (>64.5 vs <26 ng/mL) [7]. However, importantly, their stratified analyses revealed substantial

heterogeneity by preterm subtype, with elevated ferritin doubling the risk of preterm premature rupture of membranes (PPROM) (OR 2.1, 95% CI 1.1-4.1) and conferring a 2.7-fold risk of very early preterm birth (<34 weeks) when ferritin exceeded 96 ng/mL. Although our study did not subtype preterm births, the markedly higher ferritin levels observed among preterm cases are numerically consistent with Xiao *et al*.'s findings in more severe or inflammation-driven preterm phenotypes.

The inflammatory nature of ferritin is further supported by Cetinkaya *et al*. (2017), who evaluated acute-phase reactants in women with threatened preterm labor and reported significantly higher ferritin and lower albumin levels among those who ultimately delivered preterm [8]. Their findings reinforce the interpretation that ferritin elevation accompanies systemic inflammatory responses preceding preterm delivery. In our cohort, ferritin values exceeding 70 ng/mL well above typical iron-deficiency ranges were strongly associated with preterm birth, supporting this inflammatory hypothesis.

The contribution of anemia severity itself has been variably reported. Rani *et al*. (2014), in a large Indian cohort of 1,050 women, showed that increasing anemia severity independently increased the risk of preterm delivery [9]. In contrast, our study found no significant difference in hemoglobin levels or anemia severity distribution between term and preterm groups, suggesting that within an already anemic population, ferritin may capture inflammatory risk more effectively than hemoglobin alone. This divergence is numerically plausible, as Rani *et al*. compared anemic with non-anemic women, whereas our study restricted inclusion to anemic participants.

Large population-based data also support the association between high ferritin and spontaneous preterm birth. Khambalia *et al*. (2015) reported that women with ferritin levels above the 75th percentile (≥43 µg/L) and 90th percentile (≥68 µg/L) had increased odds of spontaneous preterm birth (OR 1.49 and 1.92, respectively) [10]. Notably, their reported ≥68 µg/L threshold closely approximates the 70 ng/mL cut-off identified in our study, strengthening the external validity of our findings. While their effect sizes were smaller likely reflecting a low-risk, non-anemic population the direction and threshold consistency are striking.

In contrast, Movahedi *et al*. (2012) reported lower absolute ferritin values (mean 26.7 ng/mL in preterm vs 19.8 ng/mL in term deliveries) and identified an optimal cut-off of 22.5 ng/mL with good sensitivity and specificity in an Iranian cohort [11]. The lower cut-off in their study likely reflects differences in baseline iron status, ethnicity, and assay calibration. Nevertheless, both studies including ours demonstrate that relative elevation of ferritin within a population, rather than an absolute universal threshold, is clinically meaningful.

Mechanistic explanations for these associations are well articulated by Sakata *et al*. (2008), who proposed iron-dependent oxidative stress as a central pathway in the pathogenesis of preterm birth [12]. Excess free iron, often arising from decidual hemorrhage or inflammation, promotes lipid peroxidation, DNA damage, and inflammatory gene activation—processes implicated in uterine activation and membrane rupture. Elevated ferritin in our cohort likely reflects these upstream inflammatory and oxidative pathways rather than improved iron stores.

Seminal work by Goldenberg *et al*. (1996) further supports this interpretation. In a cohort of 580 women, ferritin levels in the highest quartile at 26 weeks were associated with increased risks of preterm birth <37 weeks (OR 2.0), very preterm birth ≤32 weeks (OR 2.7), and low birth weight [13]. Importantly, hematocrit and iron deficiency were not predictive, underscoring that high ferritin not low iron signals risk, a finding mirrored in our results.

More recent Indian data by Jyothi *et al*. (2023) evaluated ferritin alongside cervical length and AFP in low-risk women and reported limited discriminatory ability (ROC AUC <0.5) [14]. This contrasts with our AUC of 0.76, which likely reflects differences in population risk profiles. Our cohort was restricted to anemic women, a group in whom inflammatory ferritin elevation may have greater discriminatory value than in low-risk populations.

Biomarker studies such as Gray *et al*. (2017) further emphasize that preterm birth is multifactorial, with shared inflammatory and metabolic pathways across spontaneous and medically indicated subtypes [15]. Ferritin may represent one component within this broader inflammatory milieu, and its utility may be enhanced when interpreted alongside clinical risk factors.

Finally, Tamura *et al*. (1996) demonstrated that women with ferritin levels above the median at approximately 24 weeks had nearly three-fold increased odds (OR 2.99) of early spontaneous preterm delivery ≤32 weeks [16]. Their conclusion that elevated ferritin reflects an acute-phase response to subclinical infection closely parallels the biological interpretation of our findings.

Taken together, our results are consistent with a substantial body of literature indicating that elevated mid-pregnancy serum ferritin is associated with increased risk of preterm birth, particularly in contexts of inflammation and anemia. While absolute cut-offs vary across populations, the consistent directionality, biological plausibility, and moderate discriminatory performance observed in our study suggest that serum ferritin may serve as a useful adjunctive marker for risk stratification among anemic pregnant women.

Limitations

This study was conducted at a single tertiary-care center with a relatively modest sample size, which may limit the generalizability of the findings to broader or non-anemic populations. Serum ferritin was measured at a single mid-pregnancy time point, and longitudinal changes in ferritin or concurrent inflammatory markers (such as C-reactive protein) were not assessed, restricting causal inference regarding inflammatory pathways. Additionally, preterm birth subtypes (spontaneous versus medically indicated) were not separately analyzed, which may have obscured etiologic heterogeneity.

Conclusion

Among anemic pregnant women, elevated mid-pregnancy serum ferritin levels were strongly associated with an increased risk of preterm birth, independent of hemoglobin concentration and anemia severity. A ferritin threshold of ≥70 ng/mL identified a subgroup with substantially higher preterm risk and demonstrated moderate discriminatory performance. These findings support the role of serum ferritin as a clinically relevant marker reflecting inflammatory processes linked to preterm delivery and suggest potential value in incorporating ferritin assessment into antenatal risk stratification for anemic women.

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