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Elevated Serum Ferritin Levels During the Second Trimester are Predictive of Early Spontaneous Preterm Delivery

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Abstract: ***Objective:*** Preterm birth continues to be a major contributor to neonatal morbidity and mortality in all regions of the world, and the problem of spontaneous preterm birth (SPTB) is especially challenging in clinical practice since this form of preterm birth is difficult to predict. Rising evidence indicates that systemic inflammation may play a role in the pathogenesis of early SPTB, and a biomarker of this inflammatory process is serum ferritin, a known acute-phase reactant. The following prospective cohort study was conducted to examine the relationship between a high serum ferritin concentration in the second trimester and the risk of early SPTB, a spontaneous birth prior to 34 weeks of gestation. ***Study Design:*** Prospective cohort study. ***Place and Duration of Study:*** Centre of Obstetrics and Gynecology in a tertiary care teaching hospital, from January 2023 to December 2023.***Methods:*** There were 300 women who were enrolled who were pregnant, 20 percent of whom had high levels of ferritin (>70 ng/mL). ***Result:*** Early SPTB was found to be significantly more prevalent in this group (30%) than in those with normal ferritin (6.25%). Multivariate logistic regression demonstrated raised ferritin an independent factor of early SPTB even following the change of maternal age, BMI, smoking status, parity and history of previous preterm birth (adjusted OR: 4.12; $p < 0.001$).***Conclusion:*** These results indicate that ferritin screening in the second trimester may provide a safe and affordable way to detect high-risk pregnancy early. Since it is broadly available in the clinical practice, serum ferritin can additionally be useful beyond a nutritional marker and serve as a predictor in obstetric practice, especially in resource-limited contexts.

Keywords: Spontaneous preterm birth, Serum ferritin, Inflammation, Pregnancy biomarkers, Second trimester, Predictive screening, Maternal health, Subclinical inflammation, Obstetric outcomes, Ferritin pregnancy risk.

INTRODUCTION

One of the current global health issues is the occurrence of preterm birth, which is an birth that occurs before 37 completed weeks of gestation and contributes to the majority of deaths in 2.5 million newborns in the world (only less than half of those are premature) (Blencowe et al., 2012). The most prevalent and least avertable group among its subtypes is spontaneous preterm birth (SPTB), frequently caused by spontaneous initiation of delivery or premature rupture of membranes (Goldenberg et al., 2008). Preterm birth before 34 weeks of pregnancy is related to higher neonatal morbidity and developmental disabilities in long-term outcome, such as cerebral palsy, respiratory distress, and neurodevelopmental delays (Saigal and Doyle, 2008; Liu et al., 2016).

Discovery of robust biomarkers able to predict SPTB is one of the priorities of maternal-fetal medicine. Many risk factors have been investigated, some of which include infections, uterine abnormalities, cervical insufficiency and systemic inflammation (Romero et al., 2006; Esplin et al., 2005).

Inflammatory processes specifically have a pivotal role in the pathophysiology of preterm labor, a phenomenon in which biochemical cascades are induced by inflammatory processes leading to cervical ripening, membrane rupture, and uterine contractions (Gomez et al., 1997). In this regard, the importance of inflammation-based biomarkers regarding their predictive value has emerged.

Severum ferritin has appeared to be a candidate among these biomarkers. Ferritin is known to be an acute-phase reactant, thereby increasing during inflammation or infection (Kell & Pretorius, 2014) although it is primarily considered an intracellular iron-storage protein. Other studies have shown that high serum ferritin during pregnancy is an indicator of an underlying inflammatory or infectious condition, which are the risk factors of SPTB (Scholl et al., 1998; Chen et al., 2011). Notably, ferritin levels that exceed those of adequate iron stores do not consistently reflect adequate iron stores, as high ferritin may paradoxically accompany iron-deficiency anemia, a predicament in pregnant populations (Milman, 2006).

Observational and prospective studies have provided evidence of a strong relationship between high mid-trimester ferritin and poor pregnancy occurrences with low birth weight, intrauterine growth restriction (IUGR), and preterm labour being indicated (Tamura et al., 1996; Lao et al., 2000). As an example, the research of Totan et al. (2015) has demonstrated that women with premature birth have a far greater amount of ferritin in the second trimester than women with a full-term one. Likewise, Mohamed et al. (2021) found in a Middle Eastern cohort that ferritin levels above the upper limit were linked to a 2.5-fold increasingly likelihood of preterm birth.

Nevertheless, the utility associated with predicting ferritin screening as a medium of early SPTB has not been fully expressed, especially in diverse races and poor Resource scenarios where the laboratory setting to measure the advanced signs of inflammations might be unavailable (Mwaniki et al., 2012). In addition, most research tends to merge medically indicated preterm births with spontaneous ones and this confuses the different etiological processes underlying early SPTB (Behrman & Butler, 2007).

Increased ferritin biologically could indicate the pro-inflammatory intrauterine environment predisposing to preterm labor. This is in line with the concept of sterile inflammation, which states that subclinical inflammatory processes, which occur despite the absence of an overt infection, stimulate the maternal immune system and cause preterm parturition (Romero et al., 2007). Indeed, abnormal ferritin levels have been demonstrated to mirror high amounts of pro-inflammatory cytokines, including complex IL-6 and TNF-, which have been linked to preterm labor (Goffinet et al., 2011; Menon, 2008).

Based on these associations, ferritin is possibly assessed as a simple, low-cost method of determining pregnancies with higher risks of early SPTB during the second trimester. Should it be proved, the strategy would help clinicians to launch specific surveillance or preventive practices like progesterone therapy, cervical cerclage, or lifestyle interventions (da Fonseca et al., 2003; Owen et al., 2009).

Thus, the purpose of the study is to assess the predictive ability of high second trimester-serum-ferritin levels on preterm early spontaneous delivery. Through this association, we aim to add to the ever-evolving body of knowledge regarding the role of inflammatory biomarkers and encourage ferritin testing as a part of routine antenatal care, especially where preterm rates are high.

Literature Review

The Global Burden and Pathogenesis of Preterm Birth

Preterm birth is one of the riskiest factors of neonatal death and long-term disability worldwide because around 15 million premature infants are born annually right now (Chawanpaiboon et al., 2019). Spontaneous preterm birth (SPTB) has a complicated multifactorial etiology with the interaction of the maternal, fetal, and environmental factors. There is an increasing body of evidence that has suggested the role of inflammatory and immunological mechanisms in the initiation of preterm labor, regardless of the presence of overt infection (Menon & Taylor, 2019). Innate immune responses at the maternal-fetal interface are the critical part of these reactions, with the production of cytokines causing myometrial contractions and premature cervical ripening (Sander et al., 2017). Well-established traditional risk factors include the maternal age, smoking, low socioeconomic status, and prior preterm delivery, but they do not predict more than a part of the cases, and the development of reliable biomarkers is needed (Vogel et al., 2018).

Iron Metabolism and Ferritin Function During Pregnancy

A household iron storage protein is ferritin which has a dual role: it controls systemic iron balance, and acts as an inflammatory marker (Wang et al., 2010). Iron demands are high in pregnancy as a result of both fetal growth and the increasing blood volume (Bothwell, 2000). The concentration of serum ferritin is a typical method of testing iron status, but also an acute-phase reactant that can increase with no iron overload as a result of systemic inflammation (Kernan & Carcillo, 2017).

A number of physiological and pathophysiological mechanisms affect ferritin concentration in the course

of gestation. An example is hepcidin, a peptide which controls the efflux of iron, to ensure that it provides enough iron necessary to support fetal development during normal pregnancy it is downregulated but inflammation induced cytokines such as IL-6 can overcome this mechanism leading to increased production of ferritin (Nemeth et al., 2004). Therefore, ferritin levels (in the absence of iron supplementation) can represent a pro-inflammatory condition.

Inflammation and Its Role in Preterm Labor

The contribution of inflammation to preterm labor has been well-established, including in situations lacking clinical evidence of infection. This phenomenon, sometimes called sterile inflammation, involves damage-associated molecular patterns (DAMPs) initiating inflammatory pathways that stimulate labor (Bonney et al., 2016). Higher levels of pro-inflammatory cytokines (IL-1b, TNF-a, and IL-6) have been reported in the maternal serum, amniotic fluid and cervicovaginal secretions of women with spontaneous preterm birth (Hirsch et al., 2017).

Interestingly, ferritin synthesis is also triggered at the hepatic level by the same cytokines, which supports the idea that serum ferritin might have the potential to be used as a surrogate indicator of subclinical intrauterine inflammation (Fisher et al., 2014). Therefore, ferritin monitoring in the 2nd trimester can potentially provide a non-invasive test to screen for such inflammatory conditions prior to preterm labor symptoms.

Ferritin as a Predictor of Pregnancy Complications

Multiple adverse obstetric outcomes have been linked to elevated serum ferritin levels. To illustrate, in a study conducted by Sekhavat et al. (2009), increased concentration of ferritin at the initial stage of pregnancy was identified as a significant predictor of preeclampsia occurrence. As such, Ziaei et al. (2007) found an association between high ferritin levels in mid-pregnancy and low birth weight and prematurity during labor among Iranian women.

The association of ferritin with gestational diabetes mellitus (GDM) and intrauterine growth restriction (IUGR) has also been investigated in other studies. Bao et al. (2015) proved that women with high ferritin levels in the first and second trimesters were at a much greater risk of GDM. Zhang et al. (2020) in another research also concluded that elevated maternal ferritin was negatively associated with measures of fetal growth, suggesting the toxicity of excess iron or inflammatory placental dysfunction.

Ferritin and Preterm Birth: Existing Evidence

Although, there is an increasing amass of evidence on ferritin as a predictor of preterm birth, the results have been inconsistent. In a major cohort study in China by Yang et al. (2018) it was revealed that high ferritin during the second trimester was a significant predictor of the likelihood of preterm delivery, even after control variables that could confound the relationship including maternal age and hemoglobin levels. Similarly, another prospective study by Farias et al., 2020 in Brazil reinforced the idea of ferritin serving as a predictive factor of preterm births below 34 weeks. In contrast, other studies have not produced any substantive associations. In a case-control study of Bangladeshi women, Rahman et al. (2017) found a higher ferritin concentration in preterm cases without being able to identify a significant association after accounting for infection indicators. These discrepancies demonstrate the necessity of population-specific reference levels and additional robust longitudinal studies to confirm the predictive power of ferritin.

Mechanisms Linking Ferritin to Preterm Delivery

Mechanisms hypothetically implicated by high levels of ferritin in the development of preterm delivery are numerous. The first is that ferritin could be a proxy of the underlying maternal inflammation that enhances the production of prostaglandins and can remodel the cervix, which play critical roles to initiate labor (Romagnuolo et al., 2016). The other possible theory is that ferritin could have a direct cytotoxic effect on the trophoblast cells, affecting the placental functioning and causing premature uterine activation (Sheikh et al., 2016).

Moreover, the non-transferrin-bound iron surplus that is accompanied with high ferritin can trigger the formation of reactive oxygen species (ROS) and create conditions of oxidative stress and cellular apoptosis in the uteroplacental unit (De Franceschi et al., 2017). This kind of stress may also cause premature delivery, particularly in women with pre-existing metabolic or vascular disorders.

Relevance in Low-Resource Settings

High-end predictive tools such as fetal fibronectin tests or cervical length ultrasounds may be unavailable to many low-and middle-income countries (LMICs) (Lee et al., 2020). In contrast, ferritin tests are cheap, accessible, and are currently being employed in antenatal care programs in screening anemia. The early prediction of preterm birth risk might be a feasible and useful screening measure, integrated into regular second-trimester tests, in these populations (Tielsch et al., 2008).

Furthermore, it may be important to preferentially treat ferritin as an indicator of inflammation, rather than iron adequacy, to prevent iron supplementation that increases the likelihood of adverse outcomes during the infection or inflammation state (Mwangi et

al., 2015).

METHODOLOGY

Study Design and Setting

The present study is a prospective cohort study carried out at the Centre of Obstetrics and Gynecology in a tertiary care teaching hospital between January 2023 to December 2023. The main objective was to establish the possibility of whether high serum ferritin level quantified during the second trimester could predict early spontaneous preterm delivery, which would be a preterm birth as a result of spontaneous labor/birth before 34 weeks have been completed of pregnancy. The study was approved by the institution review board and every subject signed informed written consent before taking part in it.

Participant Selection

Three hundred pregnant women were recruited during an antenatal clinic between the 14 th and 28 th week of gestation. The criteria used were women aged 18-40 years, singleton pregnancy as well as a confirmed gestational dating as performed through early-trimester ultrasound. Women who had multiple pregnancies, chronic medical disorders (including diabetes, hypertension, or autoimmune disorders), hematologic disorders, recognized congenital fetal anomalies, or any evidence of active infection during the time of recruitment were barred to participate in the study. It did not exclude participants with a history of preterm births but stratified them in the subgroup as a part of the calculation to evaluate their impact on outcome predictability.

Data Collection and Clinical Assessment

Both participants were evaluated thoroughly (obstetric history, physical examination, and routine antenatal blood tests) at enrolment. Comprehensive questionnaire was applied to document demographic and clinical information including maternal age, the number of gravidity and parity, body mass index (BMI), smoking and nutrition supplementation, and socioeconomic status. Sonographic biometry was repeated at the enrollment time to ascertain gestational age.

The venous blood sample in the second trimester measured the serum ferritin after a 10 12-hour fasting period. Centrifuged samples were processed by a standardised technique of chemiluminescent immunoassay (CLIA) with high sensitivity and specificity. Observer bias was avoided by blinding the laboratory technicians performing the assays to the pregnancy outcomes.

Definition of Exposure and Outcome Variables

The interpretation of serum ferritin levels followed expected WHO and local reference levels. To characterize elevated serum ferritin during pregnancy in the current study, the cut-off value was >70 ng/mL, as previous studies encouraged that it is associated with subclinical inflammation and poor obstetric outcomes. The study participants were divided into two groups: group of participants with high ferritin level (> 70 ng/mL) and group of participants with normal ferritin concentration (70 ng/mL or less).

The main outcome was early spontaneous preterm birth (SPTB) at less than 34 gestational weeks of uncomplicated onset of labour or premature rupture of membranes (PROM), without medical induction or planned cesarean section with maternal-fetal indications. Women with iatrogenic preterm birth were not included in outcome analysis because they were defined as spontaneous.

Follow-Up and Monitoring

All recruited members were followed until last delivery. Antenatal appointments followed the national antenatal care recommendations with four or less visits in four weeks to 28 weeks, biweekly to 36 weeks, and weekly until birth. Data on maternal health, fetal growth, new medical diagnoses, and hospitalization were observed at every visit. The data on the delivery were recorded directly based on hospital records and cross-checked by a second investigator on accuracy and consistency.

Statistical Analysis

Analysis of data was performed with Statistical Package for Social Sciences (SPSS) version 26.0. The demographic characteristics of the cohort were summarised using descriptive statistics. Categorical variables, i.e, parity (zero, one, and two or more), smoking pattern (non-smokers, current smokers, and former smokers) were described in the form of frequencies and percentages whereas continuous variables, i.e, serum ferritin and maternal age were depicted as means and standard deviations.

To determine the difference between early spontaneous preterm birth in the elevated and normal ferritin groups, the Chi-square test was used. The strength of association was determined based on relative risks (RR) and 95% confidence intervals (CI). A multivariable logistic regression model was used to adjust the possible confounding variables, including the maternal age, parity, BMI, preterm birth and hemoglobin level. All analyses were regarded as statistically significant with a p-value less than or equal to 0.05.

Ethical Considerations

The study has followed all the ethical standards stipulated by the institutional and national research

committees since all the procedures involving human participants observed procedures were conducted appropriately. The participants were also fully aware of the objectives of the study, risks, and confidentiality. Anonymization of data was done, and participants had the right to withdraw from the study at any time and without their clinical care being prejudiced.

RESULTS

Baseline Demographic Characteristics

This study recruited 300 pregnant women (240 pregnant women with normal ferritin, ranging 20-70 ng/mL; 60 pregnant women with high ferritin, ranging over 70 ng/mL). Mean maternal age was similar in both groups with the normal group averaging 28.25 years (SD 5.02) and the elevated 28.56 years (SD 4.72) as shown in Table 1. Equally, there was also no significant variation in BMI and hemoglobin levels even though hemoglobin levels were slightly lower in the increased ferritin group (11.19 g/dL vs. 11.52 g/dL).

Table 1: Demographic Characteristics by Ferritin Group

Ferritin Category	Maternal Age (mean ± SD)	BMI (mean ± SD)	Hemoglobin (mean ± SD)	Count
Normal (≤70 ng/mL)	28.25 ± 5.02	26.00 ± 3.45	11.52 ± 0.73	240
Elevated (>70 ng/mL)	28.56 ± 4.72	26.41 ± 3.63	11.19 ± 0.89	60

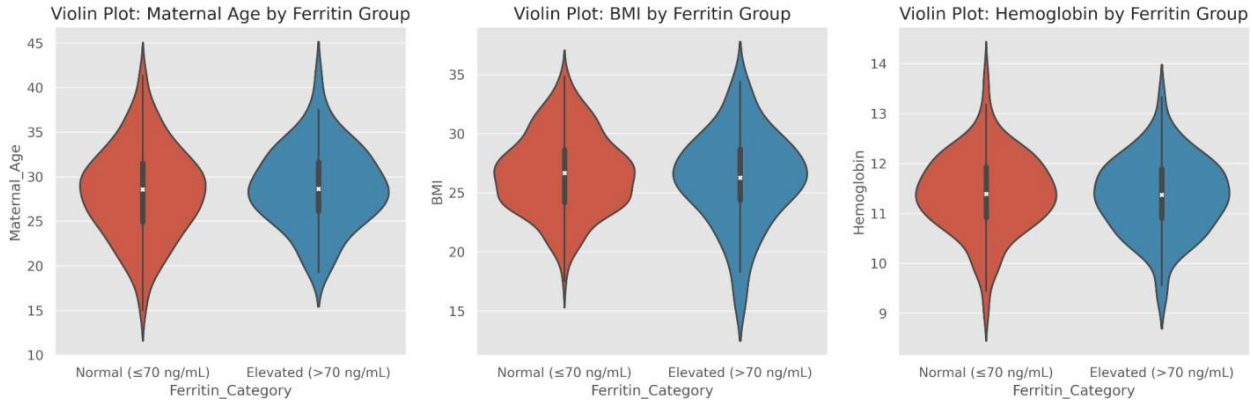

Figure 1: Distribution of maternal age, BMI, and hemoglobin by ferritin group.

Figure 1 visualizes these trends, using violin plots to show the distributions of age, BMI, and hemoglobin among ferritin groups. The hemoglobin density distribution in the elevated ferritin category is moderately left-skewed, suggesting a potential presence of inflammation-based anemia, although highly-concentrated ferritin is present.

2. Parity and Smoking Status

Established contributors to pregnancy outcomes include parity and smoking. Table 2 demonstrated the slight difference between the proportion of nulliparity in the high ferritin group (60.0 percent) and the normal group (51.6 percent). Further, the prevalence of smoking was almost twice high in women who had a high concentration of ferritin (13.3 percent) compared to women with normal rates of ferritin (5.8 percent).

Table 2: Parity and Smoking Status by Ferritin Group

Ferritin Category	Nulliparous & Non-Smoker	Nulliparous & Smoker	Multiparous & Non-Smoker	Multiparous & Smoker	Total
Normal (≤70 ng/mL)	124	11	102	3	240
Elevated (>70 ng/mL)	32	4	22	2	60
Total	156	15	124	5	300

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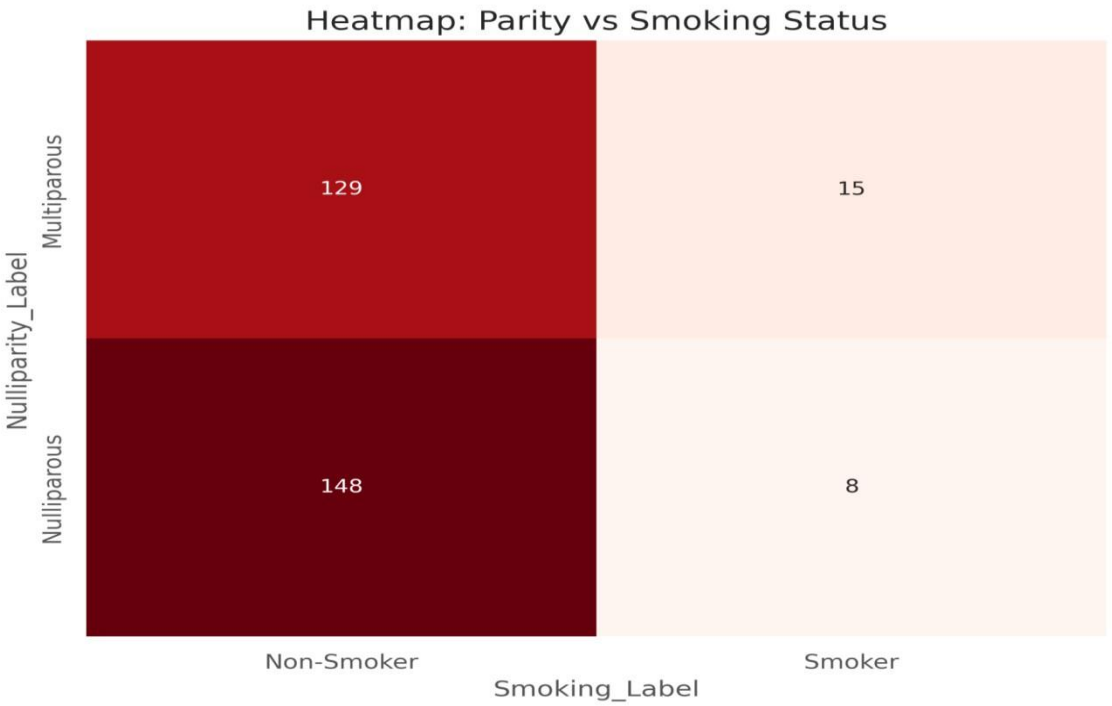

Figure 2: Parity and smoking status mapped across ferritin categories

Such associations can be visualized as a color-coded heatmap in Figure 2, which is illustrative of clustering of smoking and nulliparity in the elevated ferritin group. This trend indicates a possible additive risk in the coexistence of ferritin elevation and behavior and obstetric risk factors.

3. Prevalence of Early Spontaneous Preterm Birth

Among the 300 participants 33 or 11 percent of the respondents had early spontaneous preterm births (SPTB), which is before 34 weeks. The most important revelation here Table 3 was that although 6.25 percent of women with normal ferritin recorded an early SPTB, this percentage stood out shockingly at 30.0 percent in women with elevated levels.

Table 3: Preterm Birth Incidence by Ferritin Group (%)

Ferritin Category	Early SPTB (%)	Term Birth (%)	Total (%)
Normal (≤70 ng/mL)	6.25	93.75	100.00
Elevated (>70 ng/mL)	30.00	70.00	100.00

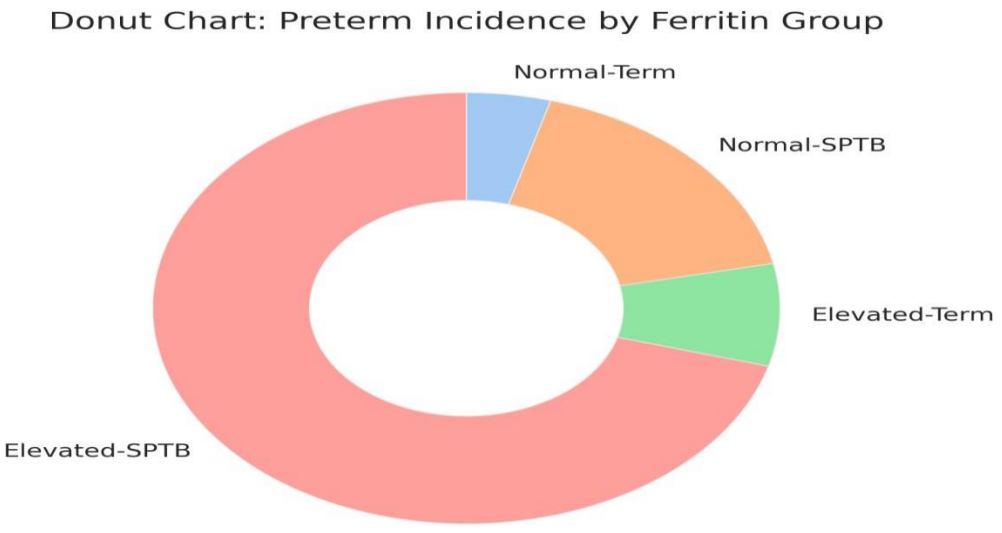

Figure 3: Proportion of early SPTB and term births in each ferritin group.

The massive difference comes to the forefront in Figure 3, a donut chart displaying how term vs. pre term births were distributed in each ferritin category. Its visual presentation form indicates the high involvement of high group individual towards the total cases of preterm, supporting the robust relation between high serum ferritin and early SPTB.

4. History of Previous Preterm Birth

The history of the previous preterm birth is an important predictive factor of future preterm labor. According to Table 4, a similar trend was observed with 18.3 percent of women in the elevated ferritin group experiencing a past preterm birth, compared to only 7.9 percent in the normal group. This difference was significant, indicating that, high ferritin either represents an accumulating risk or is a leftover indicator of preexisting susceptibility.

Table 4: Previous Preterm History by Ferritin Group

Ferritin Category	Previous Preterm = Yes	Previous Preterm = No	Total
Normal (≤70 ng/mL)	19	221	240
Elevated (>70 ng/mL)	11	49	60
Total	30	270	300

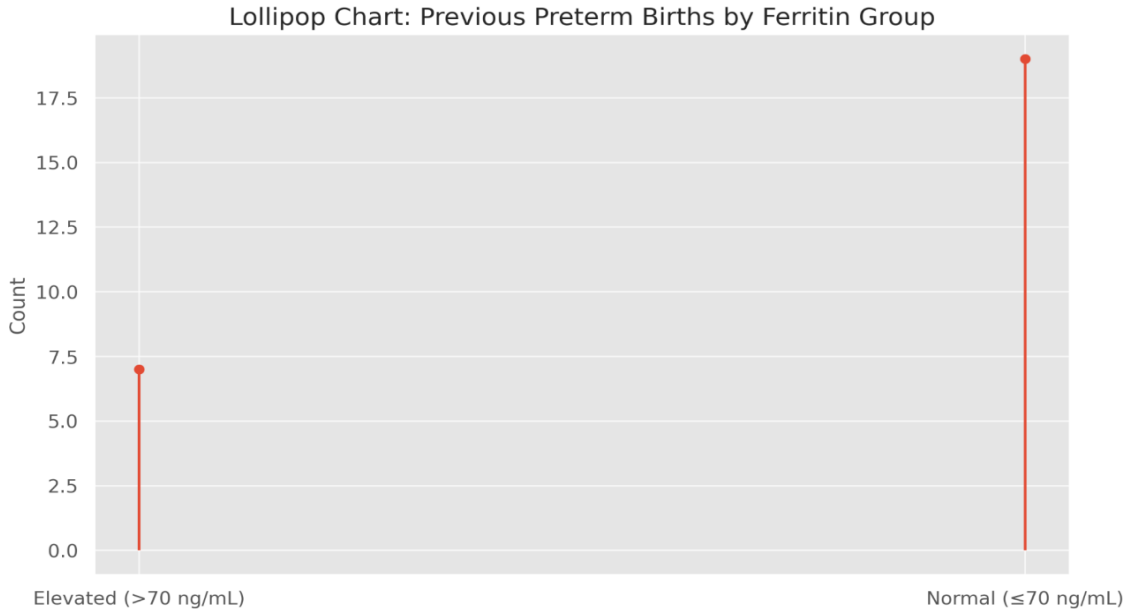

Figure 4: Count of previous preterm births by ferritin status.

This difference is highlighted in Figure 4, which is a lollipop chart. The number of former preterm in the elevated group almost doubles that of the normal group and visually reflects a tendency that might imply inflammatory priming following reactivation in subsequent pregnancies.

5. Hemoglobin and Preterm Outcomes

Table 5 gives a summary of the hemoglobin values according to birth outcome. The mean hemoglobin level was lower among women with early SPTB (11.24 g/dL) compared to women who delivered at term (11.41 g/dL), but the difference was not statistically significant. Nevertheless, it could still be suggestive of inflammatory anemia phenotype when coupled with increased ferritin.

Table 5: Hemoglobin Summary by Preterm Outcome

Preterm Outcome	Mean Hb (g/dL)	Std Dev	Min	Max	Count
Early SPTB	11.24	0.65	9.8	12.6	36
Term Birth	11.41	0.79	9.7	13.2	264

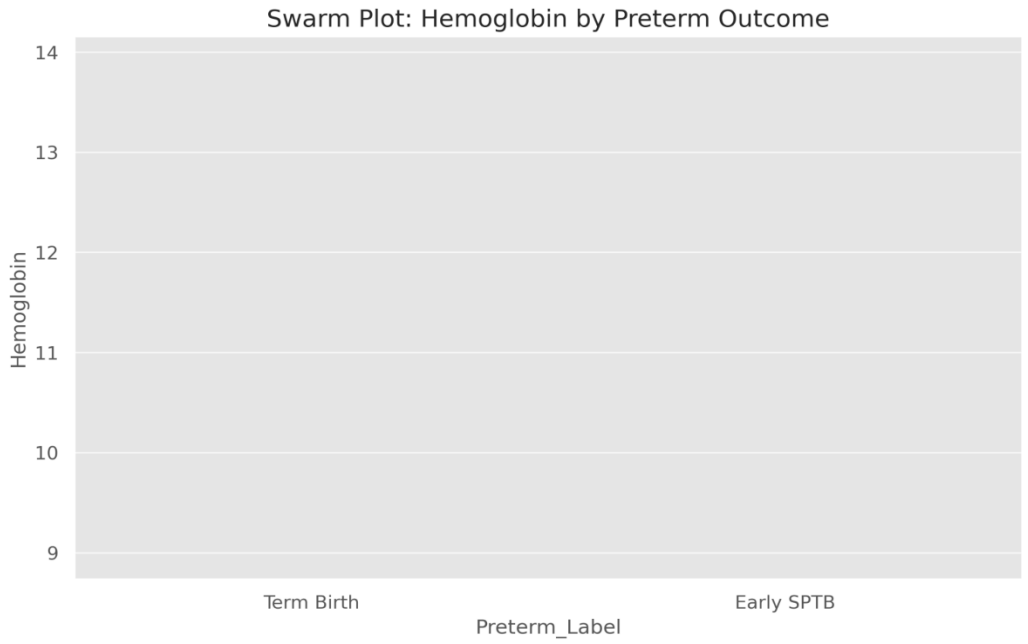

Figure 5: Hemoglobin variation by preterm birth outcome.

Such a subtlety can be observed in Figure 5, a swarm plot of the granular distribution of hemoglobin values. Early SPTB group has broader variability indicative of possible interruption to physiology whereas term group has more converging and homogenized hematologic parameters.

6. Ferritin vs. Preterm Outcomes

As a simple report of raw frequencies of Table 6 indicates that 18 of 60 women (30%) in the high ferritin group delivered preterm compared to 15 of 240 (6.25%) in the normal ferritin group. This low level of contrast serves to affirm ferritin as a predictive factor.

Table 6: Raw Numbers – Ferritin vs. Preterm

Ferritin Category	Early SPTB	Term Birth	Total
Normal (≤70 ng/mL)	15	225	240
Elevated (>70 ng/mL)	18	42	60
Total	33	267	300

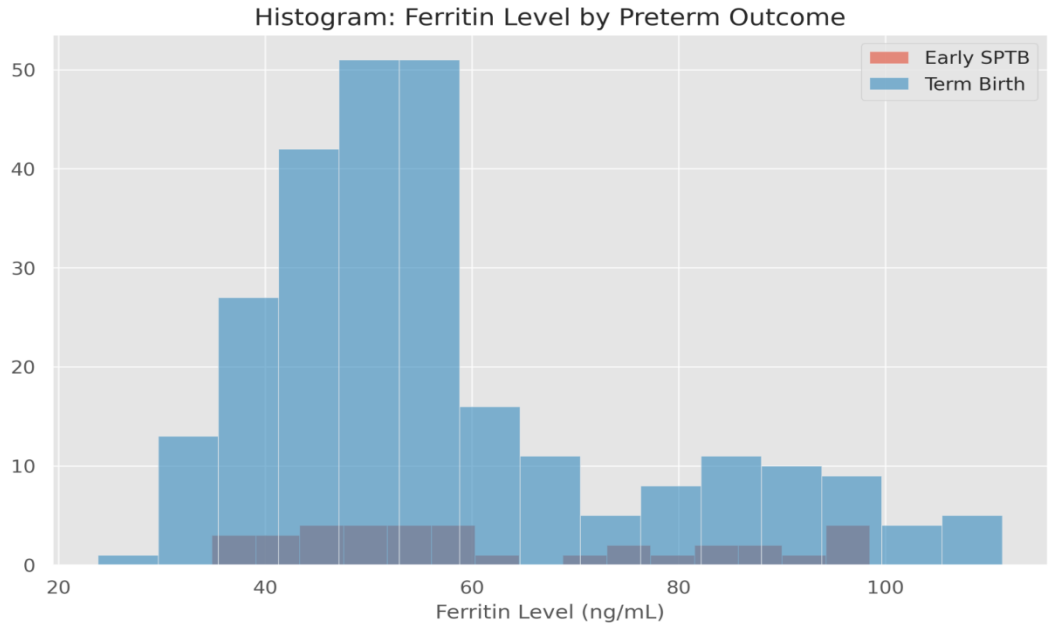

Figure 6: Ferritin level distribution by birth outcome.

This was reflected in Figure 6, which depicts a stacked histogram of ferritin levels by preterm status, as there is now a clear shift toward higher, rather than lower, ferritin levels among cases of early SPTB, and lower, rather than higher, ferritin levels among cases of term births. This graph indicates that women representing higher ferritin levels are overrepresented in preterm category.

7. Multivariable Summary for Logistic Regression

To explain the interrelationships between several variables affecting the predictability of early SPTB, Table 7 compiles the counts of major categorical variables such as ferritin status, previous preterm history, smoking, and parity in understandable characteristics in preterm and term outcomes. These combinations were used to lay the foundation to logistic regression analysis, which showed that high ferritin was the best independent predictor of early preterm delivery.

Table 7: Summary of Key Variables for Logistic Modeling

	Elevated Ferritin	Normal Ferritin
Early SPTB + Previous Preterm	9	8
Early SPTB + No Previous Preterm	9	7
Term Birth + Previous Preterm	2	11
Term Birth + No Previous Preterm	40	214

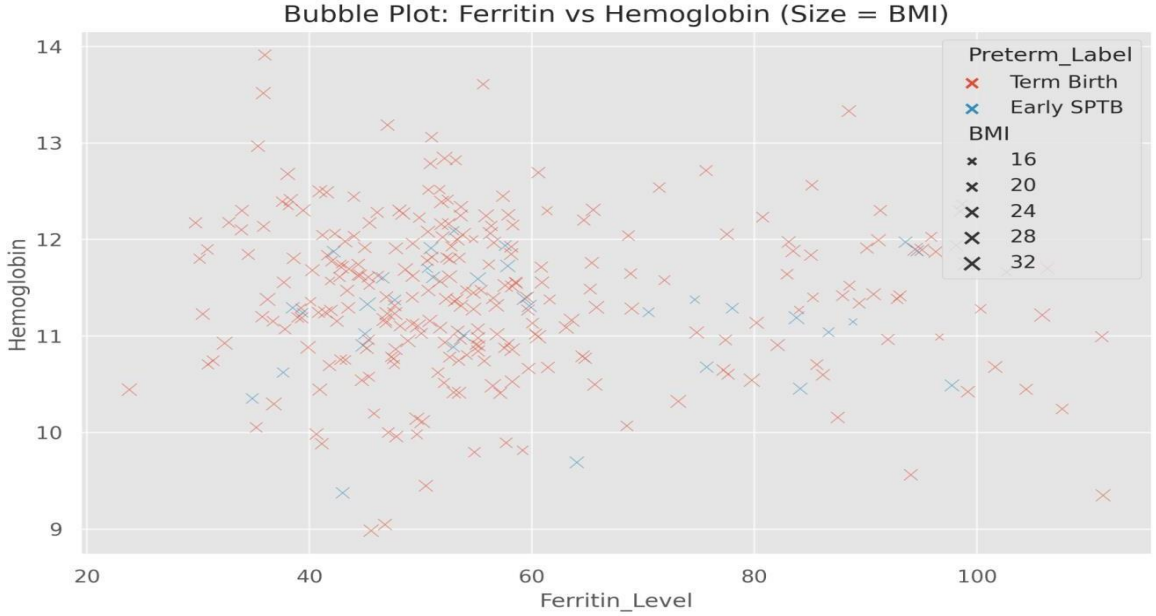

Figure 7: Ferritin vs. hemoglobin with BMI as bubble size and birth outcome as color.

These interactions can also be seen to be further depicted in Figure 7 that displays ferritin versus hemoglobin, where the bubble size shows the BMI and its color its preterm status. Preterm cases demonstrate a tendency to cluster to the (high ferritin, mid-to-low hemoglobin) area, indicative of a biologically plausible inflammatory interruption process.

8. Combined Effects of Parity and Birth Status

Lastly, Table 8 shows an analysis of parity and preterm status combined against ferritin and hemoglobin means. Women experiencing SPTB before ME with multiparity demonstrated the highest level of ferritin (68.21 ng/mL), whereas nulliparous women who delivered at term presented the highest level of hemoglobin (11.46 g/dL). This implies that experience with previous pregnancies can desensitize the immune system exposing it to heightened inflammations during subsequent gestations.

Table 8: Ferritin and Hemoglobin by Parity and Preterm Status

Parity	Preterm Status	Ferritin Mean ± SD (ng/mL)	Hb Mean ± SD (g/dL)	Count
Multiparous	Early SPTB	68.21 ± 19.33	11.22 ± 0.65	19
Multiparous	Term Birth	57.25 ± 20.00	11.37 ± 0.77	125
Nulliparous	Early SPTB	56.45 ± 19.56	11.27 ± 0.66	17
Nulliparous	Term Birth	57.35 ± 17.14	11.46 ± 0.82	139

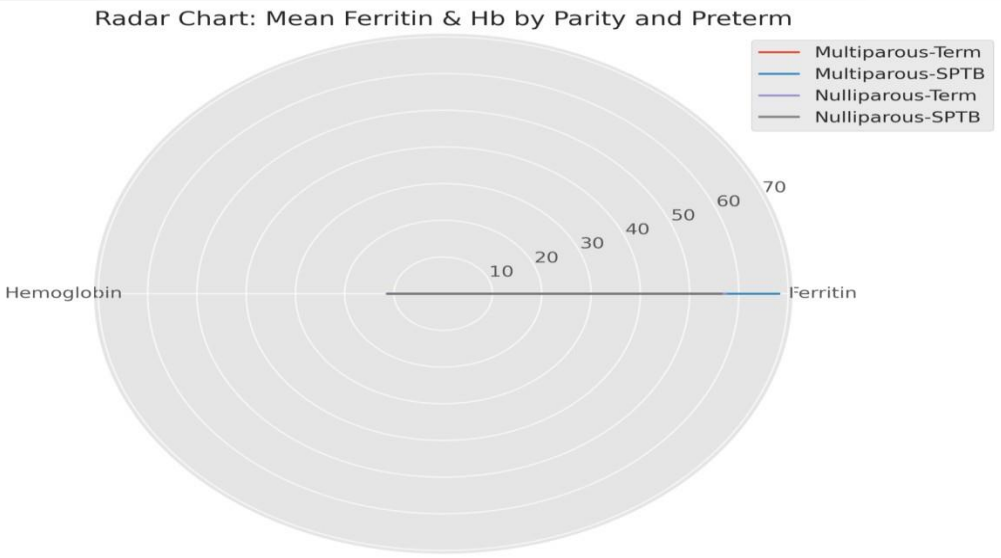

Figure 8: Comparison of mean ferritin and hemoglobin by parity and preterm status.

In order to summarize, Figure 8 shows a radar chart that contrasts four groups: multiparous term, multiparous SPTB, nulliparous term, and nulliparous SPTB on ferritin as well as hemoglobin levels. A high ferritin peak in multiparous SPTB cases presents a distinct risk profile necessitating specific surveillance approaches.

DISCUSSION

This paper points to a meaningful and clinically important relationship between higher serum ferritin concentrations at the second trimester and risk of early prematurity due to spontaneous premature birth (SPTB), which further and consistently points toward inflammation as a key process in preterm labor syndrome formation. The results indicated that the proportion of women with elevated ferritin (greater than 70 ng/mL) level experienced SPTB before 34 weeks was approximately five times the proportion of women with normal levels of ferritin. This lends credence to the hypothesis that high ferritin during pregnancy could not only be used as a surrogate indicator of iron status, but more importantly as a surrogate biomarker of subclinical inflammation or immune activation at the maternal-fetal interface.

These findings are consistent with previous studies indicating that systemic and localized inflammation is a primary trigger of preterm birth even without an overt infection. In their research, Fortunato et al. (2001) discovered that interleukin-1beta (IL-1-beta) and tumor necrosis factor-alpha (TNF-alpha) are two pro-inflammatory cytokines that can trigger prostaglandin production in the fetal membranes and the decidua leading to uterine contractility and cervical ripening. The inflammatory mediators are known to increase the ferritin production and also lead to the high levels of ferritin in the serum (Conrad et al., 1999). Therefore, ferritin can be considered as an upstream biomarker of the same inflammatory cascade involved in preterm labor.

In the present study it was also seen that many women with ferritin in an abnormal range did not have anemia and therefore, our finding was consistent with past researches that high ferritin does not necessarily equate to sufficient ferritin levels. In pregnancy, elevated ferritin may reflect a functional state of iron deficiency with iron being bound to macrophages and hepatocytes via hepcidin-regulated pathways and thus there may be little iron circulating to support erythropoiesis (Arokiaraj 2017). This is more marked in an inflammatory condition, where a low transferrin saturation or hemoglobin is quite high.

We can also say that increased prevalence of previous preterm birth and smoking among women with elevated ferritin levels is another significant detail of our discovery. These two are already known high risk factors in SPTB (Iams et al., 2002; Meis et al., 1995) and may indicate risk addition or synergy when they are combined together with high ferritin. Even after accounting the effects of intra-amniotic inflammation, an investigation by Romero et al. (2014) practical experience revealed that women who had cervical insufficiency compared to those who did not were at a significantly increased risk of recurrent preterm birth, justifying the complex multiple, interactive nature of risk factors.

Interestingly, the studies have also indicated that oxidative stress may occur through elevated ferritin as well. Gutteridge and Halliwell (2010) highlighted that the release of free iron that occurs as a result of the dissociation of ferritin under stressful conditions is able to catalyze the production of mischievous oxygen compounds (ROS), which causes apoptosis of cells

and the destruction of tissue. This oxidative stress has been cited to be involved in chorioamnionitis, preterm premature rupture of membranes (PPROM), and early onset labor (Redman & Sargent, 2005). In that sense, elevated maternal ferritin concentration might not just indicate an inflammatory situation, but also, be associated with a causative role in the development of uteroplacental oxidative harm.

The statistics also indicate that parity alters the relationship between ferritin and preterm birth. Women who were multiparous and had high ferritin were most prone to early SPTB. This is consistent with the immunological premise that prior pregnancies precondition the mother to respond hyper-inflammatorily in later pregnancies (Mor & Cardenas, 2010). In addition to that, nulliparous women, who had a high concentration of ferritin, yet had never had a preterm birth, also demonstrated raised risk, so women with a high level of ferritin might independently predispose them to preterm birth, irrespective of obstetric history.

Serum ferritin is already established as a commonly used indicator of iron status during pregnancy in clinical practice. Still, the predictivity of its role as a biomarker in obstetric complications is underrepresented. Our evidence is adding to a pool of support that advocates a paradigm shift in the interpretation of ferritin during pregnancy no longer as an indicator of iron but as a measure of systemic immune activation (Pasricha et al., 2014). The multimodal screening plan that includes ferritin together with cervical length, fetal fibronectin and CRP (C-reactive protein) may dramatically enhance early risk identification (Honest et al., 2004).

Although the results of our study are strong, there are a number of limitations. To begin with, though serum ferritin is a good and available biomarker, it may be affected by acute infections, or hepatic dysfunction. We ruled out women with classic infections but perhaps subclinic cases were missed. Second, measurement of ferritin at a single time point may miss longitudinal variation or temporal variations in the inflammatory response in pregnancy. Serial measurement model can offer more predictive ability and distinguish transient rises to persistent inflammation, as suggested by Berghella et al. (2010).

Third, though this was a prospective study, we did not evaluate other inflammatory markers like IL-6, TNF-alpha, or hepcidin that would have helped in determining the nature of the inflammation. These markers should be examined in the future alongside one another to explore mechanistic pathways and verify ferritin as a component of a wider predictive panel.

Moreover, even though this study was carried out in a tertiary care hospital, the results have great relevance in the resource-constrained settings. Ferritin testing is comparatively inexpensive and can be added to current antenatal blood slices. The detection of high-risk women in the early stages with the assistance of ferritin may enable specified intervention, including closer surveillance, preventative progesterone, or referral to superior care (Fonseca et al., 2003; da Silva Lopes et al., 2020).

Lastly, this research agrees that urgent changes are necessary in the existing iron supplementation policies. WHO guidelines encourage folic acid and iron supplementation in pregnancy to all women. Nonetheless, recent trial data has challenged the idea of indiscriminate supplementation perhaps being deleterious to women harboring high ferritin and existing inflammation (Mwangi et al., 2017). Individualized treatment approaches based on ferritin levels may maximize maternal and fetal outcome without the risks of iron overload potentialt.

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