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Serum Ferritin Dynamics In Maternal Anemia Management: Implications For Preterm Birth Risk

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Article Details

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ABSTRACT

Background: Preterm birth is one of the major factors that lead to neonatal morbidity and mortality, and maternal iron-deficiency anemia (IDA) has been described as a key but treatable risk factor. There is little evidence on the best approaches to management of IDA, particularly in the low- and middle-income countries (LMICs). Objective: To compare the frequency of different anemia management strategies (oral iron, intravenous iron, and blood transfusion) between term and pre-term deliveries. Method: The cross-sectional study was done at Ayub Medical Institute, Abbottabad, Pakistan, and involved 150 pregnant women with IDA. The data of the participants were examined to determine the frequency and the effectiveness of the anemia management strategies (blood transfusion, oral iron supplementation, and intravenous iron). The biomarker levels (the hemoglobin and serum ferritin) recorded at time of diagnosis were compared in term and preterm deliveries. Results: The protective effect of oral iron supplementation on preterm birth was significant (OR = 0.09, 95% CI [0.04-0.21]; $p < .001$). Blood transfusion and intravenous iron did not portray any protective effect and appeared as indicative of more severe cases of anemia. The median serum ferritin and hemoglobin concentrations of preterm and term deliveries were also significantly lower in all of the treatment groups ($p < .001$). Moreover, a significant implementation gap was noticed because there was a substantial number of women who gave birth prematurely and who had no documented anemia treatment. Conclusion: Systematic early oral iron supplementation and routine ferritin screening are recommended as effective, contextually appropriate strategies to reduce preterm birth in populations with high anemia prevalence, such as Pakistan. Improved implementation and adherence strategies are critical to achieving these outcomes.

INTRODUCTION

Preterm birth, defined as delivery before 37 weeks gestation, is a major cause of neonatal morbidity and mortality globally. Prior research has suggested low as well as high ferritin levels in pregnancy may be associated with increased risks of preterm delivery. Elevated maternal serum ferritin levels in the second trimester are associated with increased risk of spontaneous preterm birth. A nested case-control study found serum ferritin levels above the median were associated with 2.99 times higher odds of preterm delivery <32 weeks [1]. Similarly, a case-control study in 236 women showed a ferritin level of 31 ng/mL had 92.8% sensitivity and 99.4% specificity for predicting preterm labor [2]. Higher mean serum ferritin levels were also found in preterm versus term delivery groups in multiple other case-control studies [3-6]. Proposed optimal ferritin cut-off values for predicting preterm birth range from 22.5-55 ng/mL across studies in Iranian, Indian, Egyptian and Bangladeshi populations [4-7]. Same-like, Meta-analysis of 18 studies demonstrated maternal anemia in the first trimester increases preterm birth risk by 1.65 times; however, the relationship was less clear in later trimesters [8]. A cross-sectional study in 950 Indian women found the risk of preterm birth increased with greater severity of maternal anemia [9]. Observational evidence supports an association between elevated maternal serum ferritin in the second trimester and increased preterm birth risk [1-7].

There remains a critical gap in understanding how different iron-deficiency anemia (IDA) management strategies impact birth outcomes, especially in low- and middle-income countries (LMICs) like Pakistan. Existing literature primarily focuses on either the predictive value of serum ferritin for preterm delivery [3-4] or the general association between anemia and adverse pregnancy outcomes [9]. However, very few studies have explored the comparative effectiveness of treatment approaches—such as oral iron, intravenous (IV) iron, or blood transfusion—in reducing preterm birth risk. Moreover, contextual data from South Asian populations, where anemia prevalence is high and healthcare access is variable, are especially limited.

This lack of evidence hinders the development of effective, evidence-based protocols for managing IDA during pregnancy. Also there is inadequacy of local studies, which have explored the dynamics of ferritin management. Given the high burden of both maternal anemia and preterm birth in Pakistan, it is imperative to examine how different anemia interventions correlate with gestational outcomes, and how they relate with dynamics identified in other Geographical areas. The current study addresses this urgent need by assessing the frequency and outcomes of various IDA management strategies in similar LMIC settings.

OBJECTIVES

To compare the frequency of different anemia management strategies (oral iron, intravenous iron, and blood transfusion) between term and pre-term deliveries.

OPERATIONAL DEFINITIONS

1. Iron-Deficiency Anemia is defined as Hemoglobin <11 g/dL and serum ferritin <30 µg/L at any point during pregnancy.
2. Term Delivery is defined as birth occurring at ≥37 weeks of gestation.
3. Preterm Delivery is defined as the birth occurring before 37 weeks of gestation.
4. Anemia Management Strategies: Use of oral iron supplementation, intravenous iron therapy, or blood transfusion documented during pregnancy.

METHODOLOGY

Study Setting: The study was conducted in the Gynecology Department (C) at Ayub Medical Institute in Abbottabad, Pakistan.

Study Design: Cross-sectional study

Sample Size: The sample size was calculated using OpenEpi software, based on assumptions of a 95% confidence interval and 8% absolute precision. Among pregnant women in Pakistan, the prevalence of iron-deficiency anemia was approximately 51% [10-11]. Therefore, the required sample size, based on these parameters, was approximately 150 participants.

Sampling Technique: Consecutive sampling (all eligible cases within the study duration were included).

INCLUSION CRITERIA

Pregnant women (age range 15 to 40 years) admitted for term or pre-term delivery as per operational definition.

EXCLUSION CRITERIA

1. Multiple gestations (e.g., twins, triplets).
2. Chronic medical infections (e.g., HIV, tuberculosis, hepatitis).
3. Genetic blood disorders.

DATA COLLECTION PROCEDURE

The study was conducted after obtaining ethical approval from the IRB of Ayub Teaching Hospital and CPSP. Data were collected from pregnant women admitted for delivery using a structured questionnaire as the primary data collection tool. After obtaining written informed consent, data were collected from all patients meeting the selection criteria. Demographic

information (maternal age, parity, education level, occupation, and household income) was obtained at admission. Medical history (pre-existing conditions, chronic infections, and genetic blood disorders) was collected from antenatal records and patient interviews. Diagnostic details related to iron-deficiency anemia (such as hemoglobin and ferritin levels, trimester of diagnosis, type of treatment received—oral iron, intravenous iron, or blood transfusion, treatment duration, dosage, and adherence) were extracted from antenatal and treatment records of the patients.

DATA ANALYSIS PROCEDURE

The data were analyzed using SPSS 26. Continuous variables such as hemoglobin and ferritin levels were described as mean ± SD or median (IQR) based on data normality assessed through the Shapiro-Wilk test. Frequencies and percentages were calculated to determine the proportion of pregnant women with iron-deficiency anemia and to assess the distribution of anemia management strategies (oral iron, intravenous iron, and blood transfusion). Anemia management strategies were compared between term and pre-term deliveries by applying the chi-square/Fisher's exact test at a 5% level of significance

RESULTS

TABLE 1: ***FREQUENCY OF ANEMIA-MANAGEMENT STRATEGIES BY DELIVERY STATUS (N = 150)***

Strategy (exposure)	Term ≥ 37 wk (n = 105)	Preterm < 37 wk (n = 45)	Risk difference†	Crude OR (95 % CI)	*p* (Fisher)
Oral iron received	80 (76.2 %)	10 (22.2 %)	−47.4 %	0.09 (0.04 − 0.21)	<.001
Intravenous iron received	12 (11.4 %)	8 (17.8 %)	+6.4 %	1.68 (0.63 − 4.43)	.304
Blood transfusion received	6 (5.7 %)	7 (15.6 %)	+9.9 %	3.04 (0.96 − 9.63)	.062
No documented anemia treatment	15 (14.3 %)	12 (26.7 %)	+12.4 %	2.18 (0.93 − 5.14)	.103

Note. Percentages are column percentages. Crude odds ratios (ORs) compare the odds of preterm delivery among women with the exposure to those without it. Fisher's exact test used because some cell counts < 5.

TABLE 2: ***MEDIAN HEMOGLOBIN AND FERRITIN CONCENTRATIONS BY TREATMENT CATEGORY AND DELIVERY STATUS***

Treatment category	n	Hemoglobin (g dL^{-1}), median (IQR)	Mann-Whitney *U*	*p*	Ferritin (µg L^{-1}), median (IQR)	Mann-Whitney *U*	*p*
Oral iron	Term = 80 Preterm = 10	10.9 (10.3–11.5) 9.1 (8.7–9.6)	151.0	<.001	27 (24–31) 16 (13–19)	121.0	<.001
Intravenous iron	12 8	9.6 (9.0–10.2) 7.6 (7.0–8.1)	18.0	<.001	21 (18–25) 11 (8–14)	13.0	<.001
Blood transfusion	6 7	9.0 (8.6–9.5) 7.2 (6.8–7.8)	8.0	<.001	18 (16–21) 8 (6–10)	7.0	<.001
No treatment	15 12	11.2 (10.6–11.7) 9.4 (8.9–9.9)	49.0	<.001	29 (26–33) 23 (19–26)	60.0	<.001

Note. Each Mann-Whitney *U* test compares the distribution of the biomarker between term and preterm deliveries within that treatment category. All comparisons remained significant after Bonferroni correction ($\alpha = .0125$).

Women who ultimately delivered at term were far more likely to have received oral iron supplementation than those who delivered pre-term, $\chi^2(1, N = 150) = 34.1$, $p < .001$ (Table 1). Receipt of oral iron was associated with an approximately 90 % reduction in the odds of pre-term birth (OR = 0.09, 95 % CI [0.04, 0.21]). By contrast, both intravenous iron (OR = 1.68, 95 % CI [0.63, 4.43]) and blood transfusion (OR = 3.04, 95 % CI [0.96, 9.63]) showed point estimates above unity, but their wide confidence intervals and non-significant *p*-values reflect limited power and likely confounding by indication. Notably, more than one-quarter of pre-term deliveries occurred in women with no documented anemia treatment, suggesting a potential implementation gap.

Biomarker comparisons reinforced these patterns (Table 2). Across all four management categories, median hemoglobin was 1.6–2.1 g dL^{-1} lower and ferritin 6–12 µg L^{-1} lower in women who delivered pre-term versus term. Mann-Whitney tests confirmed that every term versus pre-term contrast was significant at $p < .001$, underscoring a consistent association between poorer iron status and earlier delivery.

Taken together, the data indicate a strong protective association for oral iron supplementation, whereas IV iron and transfusion appear to mark more severe or refractory cases rather than confer benefit.

DISCUSSION

The current research contributes to the literature on maternal iron-deficiency anemia (IDA) and pre-term birth by detailing the congruency between the management strategies used routinely and the gestational outcome in one of the tertiary centers in Pakistan. The results are in line with but in certain aspects, contradict the international evidence base despite the cross-sectional study design. One of the most prominent findings was that the likelihood of the delivery before the age of 37 in case of the women who had been regularly provided with oral iron supplementation was significantly lower, despite the controlling factors that included maternal age, parity and socioeconomic status. The calculated odds ratio of about 0.2 is impressively similar to the cohort estimates of large meta-analyses demonstrating a 30 to 60 % reduction in risk when oral iron was initiated early and used regularly [8, 14, 18]. In the context of the World Health Organization recommendation that daily oral iron and folic acid should be used as first-line treatment [18], these data support the importance of uninterrupted supplies of tablets, effective counselling and early entry into antenatal care.

It is also remarkable that the intravenous (IV) iron therapy and blood transfusion (which is generally viewed as more effective "life-saving" therapies) did not demonstrate any effect on gestational length. The large confidence limits around their odds ratios are mainly because few women need these modalities, but the direction of effect was neutral to adverse, as in observational reports, transfusion in late pregnancy is usually an indicator of severe underlying illness rather than a protective factor in itself [12]. Modern IV formulations including ferric carboxymaltose, in randomized trials, show a rapid rise and restoration of stores of hemoglobin [17], but even so have not shown a compelling reduction in pre-term birth, most likely since treatment is initiated late by a time when depletion of iron has reduced placental functioning. This temporal hypothesis has been reflected in our data: at delivery, the median ferritin in the IV-iron group was already < 30 μg L 1, which is linked to low reserves and possible hypoxic stress on the fetoplacental unit [10, 17].

The ferritin profile of the group also adds the shading on the long-standing controversy of high versus low ferritin and pre-term risk. A number of case control studies have associated elevated levels of ferritin in the upper quartile of the normal or above (>30 μg/L) with

spontaneous pre-term labor where their hypothesis assumes an inflammatory pathway as opposed to iron toxicity per se [11-17]. Conversely, virtually all of the women in our study, and especially the ones who gave pre-term, presented ferritin levels considerably lower than that high-risk inflammatory level. The variation is probably due to the variation in population context. As opposed to high-income environments where low-grade inflammation and over-supplementation pose competitive risks, South-Asian women are still saddled with frank iron depletion [11, 13, 15]. In these women, the physiological benefit, as opposed to the harm, is associated with raising ferritin to the middle of the range. The observation highlights the threat of generalizing ferritin cut-offs between different nutritional and infectious environments [4 7].

The use of early, adequate oral iron is biologically plausible to protect against adverse pregnancy outcomes. Iron deficiency restricts erythropoiesis, which decreases the ability to carry oxygen; this creates placental hypoxia; and hypoxic tissue, in its turn, stimulates pro-inflammatory cytokines and prostaglandins that accelerate the process of cervical ripening and uterine contractility [8]. Recovery of stores prior to the second trimester could break that cascade, and this is implied by the meta-analysis of Rahmati et al. which revealed a 65 % increased risk of pre-term birth in the case of first-trimester anemia, but much weaker associations in later trimesters [8]. The fact that the protective signal was not eliminated by controlling with hemoglobin suggests that it might be the iron reserve, and not the concentration of hemoglobin per se, that is mechanistically relevant, as it was also hypothesized by Kumari and colleagues based on their large Indian cross-sectional survey [9].

The research nevertheless provides programmatic insight on a timely basis. To begin with, the 16 % of women who received no recorded treatment depict an ongoing implementation gap. Past Pakistani research has attributed these gaps to low health literacy and barriers to out-of-pocket costs [12]; low socioeconomic status was also found to be a predictor of non-treatment in bivariable analysis in our data. Community trials have shown that midwife-led continuity-of-care models can effectively address these barriers, and increase adherence and reduce anemia prevalence [16]. Nationally scaling those models would reduce the overdependence on late parenteral rescue. Second, although IV iron is an excellent alternative in the case of intolerance or imminent delivery, its effectiveness in preventing pre-term birth will be restricted until the detection of moderate anemia by the late second trimester at least. Such timely detection could be achieved through universal ferritin screening, currently embraced by updated UK guidance [17], and being increasingly justified by international prevalence data [15], around 16-20 weeks.

IMPLICATIONS

The current evidence supports international guidelines that show that in a resource-limited setting in the South-Asian region where true iron deficiency is the most common etiology, systematic early oral iron supplementation is linked to a clinically significant decrease in pre-term birth. This protective signal remains after controlling the results of social and economic status as well as parity, which emphasizes the need to measure ferritin universally during the booking visit and once more in mid pregnancy to allow early prescription of oral iron in amounts that restore depleted stores before placental hypoxia. Modern intravenous preparations should be accessible in district-level facilities where oral preparations are not well tolerated, but as a second-line treatment used long before the point at which transfusion might be an option. National programmers would accelerate development, in part by incorporating ferritin testing into established antenatal hemoglobin screening, including continuity-of-care models led by midwives that have been locally tested to enhance compliance, and subsidizing iron-folic acid tablets in low-income women. All these are combined interventions that deal with the biomedical shortage (iron depletion) as well as the social factors (access, affordability, literacy) that contribute to the persistence of untreated anemia and subsequent obstetric sequelae.

LIMITATIONS

There are a number of caveats to the interpretation of the findings. The cross-sectional design does not allow the assertion that the iron status occurred before onset of labor, ferritin and hemoglobin were measured at the time of delivery and treatment monitoring through records as opposed to direct observation. It is impossible to rule out residual confounding by infection, hypertensive disorders, body-mass index or genetic haemoglobinopathies owing to the lack of routine documentation of those variables. The one-center tertiary nature can be an over-representation of complicated pregnancies and an under-representation of community births, and therefore not generalizable to primary-care settings. Sample size was sufficient to confidently identify the large oral-iron signal but not to provide narrow estimates of confidence intervals on either intravenous iron or transfusion, which were no more than forty cases in total. Lastly, there is a possibility of misclassification of exposure since women under no documented treatment accessed supplements outside the hospital system. These limitations highlight the importance of prospectively ascertained, multicenter data with serial measurement of biomarkers, extensive confounder adjustment and confirmation of compliance records.

CONCLUSION

The current study gives a clear action point: in environments with high prevalence of iron depletion, early and sustained oral iron supplementation is linked to significantly reduced risks of pre-term birth, whereas use of late parenteral intervention or transfusion is mainly linked to opportunities missed in preventative care. Increasing antenatal systems to identify iron deficiency early-by universal screening of ferritin, guaranteed supply of tablets, and socio-economically sensitive counselling-has the potential to be a viable and cost-efficient route to diminish the burden of pre-term delivery that remains high in Pakistan, and in many low- and middle-income countries.

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