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Investigating the Association between Maternal Iron Supplementation and Neonatal Jaundice

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ABSTRACT

Neonatal hyperbilirubinemia, being the most common cause of admission in the neonatal period, remains a global burden, especially in low- and middle-income nations. Addressing the mother's risk factors for neonatal jaundice was crucial for delivering better neonatal healthcare. One possible risk factor for neonatal hyperbilirubinemia is maternal iron supplementation. **Objective:** To analyze the effect of maternal iron supplementation as a risk factor for neonatal hyperbilirubinemia. **Methods:** In this prospective cohort study, using convenience sampling women with prenatal appointments during the first trimester of their pregnancies were evaluated and placed on therapeutic and prophylactic iron supplementation. Women were grouped on basis of serum ferritin level. Injectable Iron were given to women not improving with oral iron. The primary outcome was proportion of neonates developing hyperbilirubinemia during the first week of life. Data analysis was done using SPSS version 23.0. Normality of the data was checked by Shapiro-Wilk test. Chi-squared test was applied to compare variables between groups. Regression analysis was conducted to find the association between maternal iron supplementation and neonatal hyperbilirubinemia. **Results:** A sample of 176 mothers participated in the study. The overall frequency of newborn hyperbilirubinemia was 50.6%. The odds of having hyperbilirubinemia were 5.5 times higher with injectable iron. (aOR 5.5 95%CI:1.36-22.33). **Conclusion:** The outcome highlighted the potential connection between the iron supplementation of the mother during pregnancy and the development of neonatal jaundice suggesting the need to exercise early intervention in pregnant mothers who were at high risk of newborn jaundice.

INTRODUCTION

Neonatal hyperbilirubinemia (or neonatal jaundice) is a common condition that carries the risk of severe and life-threatening complications [1]. It is the most common cause of hospitalization in the neonatal period and affects up to 60% of neonates born at term [2, 3]. Although usually benign, hyperbilirubinemia results in significant neonatal morbidity and mortality, especially in low-income and middle-income countries [4, 5]. In Pakistan, the reported frequency of neonatal hyperbilirubinemia varies considerably and large-scale population-based studies are lacking. The latest available estimate comes from a population-based prospective study that reported a prevalence of 27.6% [6]. Maternal anemia, especially iron-deficiency anemia, is a significant concern in developing countries, including Pakistan, where it affects around 40-75% of women of reproductive age [7]. It is associated with several adverse neonatal outcomes, such as preterm birth, low birth weight, and perinatal mortality [8]. To decrease the risk of maternal anemia, the WHO recommends daily iron supplementation (30-60 mg of elemental iron) in pregnant women [9]. However, excessive iron supplementation can result in iron overload, which may negatively affect neonatal outcomes [10, 11]. Study have shown that higher iron intake in mothers can lead to increased incidence of neonatal jaundice [12]. Various risk factors for neonatal hyperbilirubinemia have been reported

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in the literature, including certain genetic diseases, inborn errors of metabolism, maternal diabetes, family history of jaundice, mode of delivery, delayed cord clamping, infections, sepsis, and prematurity [2, 13]. More recently, maternal iron supplementation has emerged as a potential risk factor for neonatal hyperbilirubinemia [14]. Recent studies have revealed associations between maternal and fetal hemogram aberrant maternal blood parameter levels as an indicators of newborn jaundice but the links and mechanism between maternal iron supplementation and neonatal jaundice is still poorly understood [15, 16]. Furthermore, research data supports the notion that sociocultural, seasonal, and ethnic variables also affect the development of neonatal jaundice [17]. To the best of our knowledge, this association has not been explored in our population yet.

Therefore, it was aimed to investigate the association of iron supplementation of pregnant females for both therapeutic and prophylactic purposes with neonatal hyperbilirubinemia.

METHODS

This was a prospective cohort study conducted at Darul Sehat Hospital for a period of 6 months (March 2022 to Aug 2022) after the approval from institutional review board, DSH/IRB/2022/0013. Women coming for antenatal visit in the first trimester of pregnancy and delivering at term were included in the study. Women with comorbidities (hypertension, diabetes, renal and liver disorders), blood transfusion in pregnancy and Rh negative women were excluded. Babies of mothers with Rh and ABO incompatibility, G6PD deficiency, and those delivering <35 weeks were also excluded. Women who attended prenatal appointments during the first trimester of their pregnancies were recruited using convenience sampling and evaluated by sending Complete blood counts during first trimester. Women with Hemoglobin less than 11 gm/dl were placed on therapeutic oral iron while mothers with Hemoglobin >11 gm/dl were placed on prophylactic oral iron supplementation according to the guidelines [9]. At 36 weeks of gestation, a repeat complete blood count was performed along with serum ferritin levels. Women were grouped on basis of serum ferritin level < 15 microgram per liter and serum ferritin level > 15-30 microgram per liter. Injectable Iron were given to women not responding to oral iron. Maternal anemia was classified as mild, moderate, and severe as per WHO classification [18]. The primary outcome was proportion of neonates developing hyperbilirubinemia during the first week of life. The bilirubin levels were interpreted in accordance with the neonate's age in hours according to the current guidelines [19]. Data were collected by trained junior doctors, after taking verbal informed consent on a pretested structured questionnaire based on literature review which included sections on maternal demographics, medical history, iron supplementation details (including type, dosage, frequency, and duration), and neonatal outcomes. Maternal investigations included complete blood count (1st trimester and 36 weeks) and serum ferritin levels. Neonatal outcome included were gestational age, mode of delivery, birth weight, and APGAR score. Content validity was assessed by having a panel of experts from Gynaecology and Pediatrics to evaluate the questionnaire to ensure that it adequately covered all aspects. Face validity was evaluated by piloting the questionnaire with a small sample of 20 pregnant women similar to the study population. It was carefully considered potential confounders and biases to ensure the validity of our findings. To address confounding factors, it was recognized that pre-existing maternal health conditions, such as diabetes, hypertension, and hypothyroidism, which could influence both the need for iron supplementation and the risk of neonatal jaundice. These conditions were meticulously recorded at the study's outset, and were excluded. Additionally, gestational age and birth weight, known risk factors for neonatal jaundice, were included as covariates, with subgroup analyses conducted to explore their specific effects. To minimize biases, it took several precautions. Information bias was mitigated by verifying iron supplementation through prescription records and diagnosing neonatal jaundice using standardized clinical criteria. It was also reduced recall bias by collecting data prospectively during routine antenatal visits, rather than relying on retrospective self-reporting. These comprehensive measures ensured that our study findings were both robust and reliable, providing valuable insights into the potential link between maternal iron supplementation and neonatal jaundice. It was hypothesized that there was a significant association of maternal iron supplementation on neonatal bilirubin levels. The minimum sample size n = 84 was calculated by the WHO sample size calculator 2.0, using two sample situations: 2.2b hypothesis test for two populations proportions, with a 95% confidence interval, with 27.6% prevalence of iron supplementation in cases and 8.5% in control in pregnant females of Pakistan [6]. A total of 176 mothers and their neonates were included in the study based on eligibility criteria. Data analysis was done using SPSS version 23.0. Normality of the data was checked by Shapiro-Wilk test. Due to non-normal distribution of all continuous variables, they were presented as median (interquartile ranges) while categorical variables were presented as frequencies (percentages). Mann-Whitney U test and Chi-squared test were applied to compare variables between groups. Regression analysis was conducted to find the association of neonatal hyperbilirubinemia and maternal supplementation. P-value<0.05 was considered to be statistically significant.

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RESULTS

A total 176 pregnant women participated in the study with a median age of 30 years (25-33). More than half of mothers were mild anemic 99(56.2%) and 12 (6.8%) were moderately anemic as shown in figure 1.

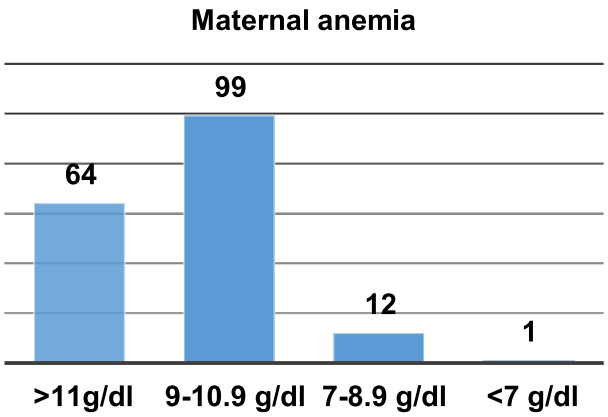

Figure 1: Distribution of study participants according to Maternal Anemia

Table 1 showed association of serum ferritin levels of women with their baseline characteristics and biochemical parameters. Maternal age was significantly lower among those with ferritin level 15-30 mcg/L (p-value<0.05) whereas, hemoglobin, hematocrit, and MCHC of women at 3rd trimester was significantly higher in women with ferritin level 15-30 mcg/L (P-value<0.05). Moreover, significant association was found between maternal serum ferritin and the type of iron supplements. A significantly higher proportion of women with serum ferritin <15 mcg/L received injectable iron supplements (29.9%) compared to those with ferritin level 15-30 mcg/L (12.4%). Data presented as n (%) or median (interquartile range): p-value<0.05 considered to be statistically significant.

Table 1: Association of Maternal Serum Ferritin Level with Baseline Characteristics and Biochemical Parameters

Variables	Serum Ferritin <15 mcg/L N (%)	Serum Ferritin 15-30 mcg/L N (%)	p-Value	Overall
n	87	89	-	176
Maternal Age	30 (27-34)	29 (25-32)	0.005	30 (25-33)
Gravida	3 (2-4)	2 (1-4)	0.15	2 (1-4)
Hemoglobin at Booking Visit	10 (9.5-11)	10.5 (9.7-11.65)	0.149	10 (9.6-11.2)
Hemoglobin in 3rd Trimester	10.2 (9.7-11.2)	10.8 (10.2-11.45)	<0.0001	10.5 (9.925-11.3)
Hematocrit in 3rd Trimester	32 (30-33)	33 (31-35)	0.032	32 (31-34)
MCV in 3rd Trimester	82 (75-87)	84 (80-88)	0.07	82.5 (79-87)
Peripheral Film in 3rd Trimester				
Normocytic Normochromic	50 (57.5%)	67 (75.3%)	0.057	117 (66.5%)
Normocytic Hypochromic	2 (2.3%)	3 (3.4%)		5 (2.8%)
Microcytic Hypochromic	29 (33.3%)	13 (14.6%)		42 (23.9%)
Normochromic Anisocytosis	5 (5.7%)	4 (4.5%)		9 (5.1%)
Mode of Delivery				
Normal Vaginal Delivery	32 (36.8%)	29 (32.6%)	0.954	61 (34.7%)
Instrumental VaginalDelivery	1 (1.1%)	1 (1.1%)		2 (1.1%)
Elective LSCS	34 (39.1%)	38 (42.7%)		72 (40.9%)
Emergency LSCS	19 (21.8%)	19 (21.3%)		38 (21.6%)
VBAC	1 (1.1%)	2 (2.2%)		3 (1.7%)
Iron Supplementation				
Oral Iron	61 (70.1%)	78 (87.6%)	0.004	139 (79%)
Injectable Iron	26 (29.9%)	11 (12.4%)		37 (21%)

Table 2 highlighted 64 (36.3%) mother with no anemia were receiving oral iron and 25 (67.5%) mothers who were mildly anemic received injectable iron.

Table 2: Association of Maternal Anemia with Iron Supplementation

Maternal Hemoglobin	Iron Supplementation N (%)		p-Value	Overall N (%)
	Oral Iron	Injectable Iron		
>11	62 (44.6%)	2 (5.4%)	<0.001	64 (36.3%)
9-10.9	74 (53.2%)	25 (67.5%)		99 (56.2%)
7-8.9	2 (1.4%)	10 (27.0%)		12 (6.8%)
≤7	1	0		1
Total	139 (79%)	37 (21%)		176

Table 3 signified that 37 (21%) neonates developed substantial Jaundice but statistically not significant p value > 0.05, whereas 13 (79%) babies were born with normal weight and 157 (89.2%) babies has good apgar.

Table 3: Effect of Maternal Hemoglobin on Neonatal Outcome

Neonatal Outcomes		Mother Hemoglobin in 3rd Trimester mg/dL				Total
		>11	9-10.9	7-8.9	<7	
Total Bilirubin of Neonates N (%)	<9.9	28	38	0	0	66(37.5%)
	10-15.9	24	41	7	1	73(41.5%)
	16-19.9	10	18	5	0	33 (18.8%)
	>20	2	2	0	0	4 (2.3%)
Total	-	64	99	12	1	176
p-value	-	0.220				-
Weight of Baby at Birth N (%)	<1.5	0	2	1	0	3 (1.7%)
	1.6-2.4	8	14	2	1	25 (14.2%)
	2.5-3.5	55	75	9	0	139 (79.0%)
	>3.5	1	8	0	0	9 (5.1%)
Total	-	64	99	12	1	176
p-value	-	0.094				-
Apgar Score of Baby N (%)	4-6	6	12	1	0	19 (10.7%)
	>7	58	87	11	1	157 (89.2%)
Total	-	64	99	12	1	176
p-value	-	0.450				-

Overall, the frequency of neonatal hyperbilirubinemia was found to be 89(50.6%) while 83 (47.2%) neonates were admitted to NICU as showed in figure 2.

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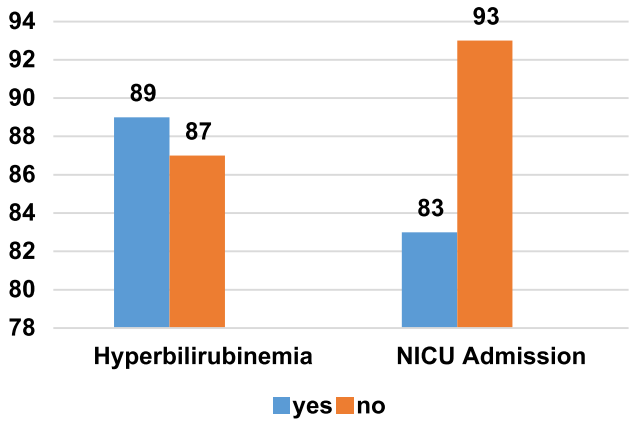

Figure 2: Frequency of Neonatal Hyperbilirubinemia and Neonatal Admission

Table 4 presented the frequency of neonatal hyperbilirubinemia among women using oral iron supplements or injectable iron supplements. The incidence of neonatal hyperbilirubinemia was notably higher among women using injectable iron supplements compared to those who received oral iron supplements (83.8% versus 41.7%; P-value <0.001). Data presented as n (%): p-value<0.05 considered to be statistically significant

Table 4: Frequency of Neonatal Hyperbilirubinemia among Women Receiving Oral Iron or Injectable Iron Supplements

Maternal Hemoglobin	Oral iron N (%)	Injectable iron N (%)	p-Value	Overall N (%)
n	139	37	-	176
Hyperbilirubinemia				
No	81 (58.3%)	6 (16.2%)	<0.001	87 (49.4%)
Yes	58 (41.7%)	31 (83.8%)		89 (50.6%)

Regression analysis (table 5) shows a significant association between neonatal hyperbilirubinemia and maternal iron supplementation. Initially, there was a robust association (crude odd ratio of 7.22), which remained statistically significant after adjusting for various parameters (adjusted odds ratio of 5.5). The odds of having hyperbilirubinemia with injectable iron supplements was 5.5 times higher than those receiving oral iron supplements (Table 4)(OR 5.5 95% CI 1.36-22.33, p = 0.017). CI: confidence interval; adjusted for ferritin, maternal age, gravidity, parity, Hb at booking visit, Hct at booking visit, MCV at booking visit, Hb at 3rd trimester, Hct at 3rd trimester, MCV at 3rd trimester.p-Value<0.05 considered to be statistically significant.

Table 5: Association of Maternal Iron Supplements and Neonatal Hyperbilirubinemia

Iron Supplements	Crude OR (95% CI)	p-Value	Adjusted OR (95% CI)	p-Value
Oral Iron	1	-	1	-
Injectable Iron	7.22 (2.83-18.42)	<0.001	5.5 (1.36-22.33)	0.017

DISCUSSION

The frequency of neonatal hyperbilirubinemia in our study was around 50%, which was similar to the results of a hospital-based cross-sectional study from Ethiopia where the prevalence of neonatal hyperbilirubinemia was 42.3% [20]. However, it was considerably higher (27.6%) than that reported by Tikmani SS *et al.*, in their population-based prospective study from Pakistan [6]. The difference could be due to different set of population, study design, sampling size, and methodology. Our hospital-based study allowed us to monitor the newborns for jaundice because the mothers received regular prenatal care up until delivery and were followed thereafter on post-natal visits. Iron supplementation to prevent the risk of anemia in pregnant women has been a concern as maternal anemia has several adverse consequences in infants, including low birth weight, preterm delivery, and increased susceptibility to infections. However, recently concerns have been raised regarding the adverse effects of iatrogenic iron overload [10, 21]. A nested case-control study by Mohammad Ali Moghimi MA *et al.*, compared excess iron supplementation may be associated with neonatal hyperbilirubinemia and jaundice [12]. The underlying pathophysiology was believed to be related to the alteration of heme metabolism due to iatrogenic overload as a result of iron supplementation [22]. Our study highlighted those 61 (34.6%) babies of mothers with mild anemia experienced considerable jaundice, with two of them developed severe jaundice. The reason could be attributed to use of injectables iron in mildly anemic mothers when oral iron can easily be used along with dietary modifications. Other minerals such as zinc have also been reported to influence bilirubin levels. Zinc inhibits heme oxygenase, resulting in decreased bilirubin levels [23]. Iron, on the other hand, increases the expression of heme oxygenase, which may result in hyperbilirubinemia [22]. Our study showed a strong association between neonatal hyperbilirubinemia and iron supplementation. This finding was also corroborated by the results of a randomized double-blind trial, which studied birth outcomes of iron supplementation in mothers and showed a higher incidence of neonatal jaundice in those that had received supplementation compared to those that had not. It should, however, be noted that this trial included women with a high baseline hemoglobin (>13.2 g/dL). Moreover, only the incidence of physiologic jaundice was noted and neonates with pathologic jaundice were excluded [14]. Our study was one of the first local study to explore the association between iron supplementation and neonatal hyperbilirubinemia. However, a few limitations should be noted. It was a single-center study and hence the findings may not be generalizable to other populations. Other potential risk factors like socioeconomic condition, parent's income and maternal weight/BMI were not included in the study. Moreover, we could not establish causality as it was a cohort study.

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CONCLUSIONS

The outcome highlighted the potential connection between the iron supplementation of the mother during pregnancy and the development of neonatal jaundice and suggests the need to exercise caution when prescribing iron supplements to pregnant women. Pregnant mothers who were at high risk of newborn jaundice should receive early intervention. Multi-center, larger-scale studies should be conducted to further investigate and validate our findings.

Authors Contribution

Conceptualization: SQB, SAM
Methodology: SQB, SAM, ANA, NS
Formal analysis: SQB, SAM
Writing, review and editing: SQB, SAM, ANA, NS

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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