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IMPACT OF IRON SUPPLEMENTATION FREQUENCY ON MATERNAL AND PERINATAL OUTCOMES IN MILD TO MODERATE ANAEMIC PREGNANT WOMEN: AN OBSERVATIONAL ANALYSIS

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ABSTRACT

Background: Iron deficiency anaemia (IDA) remains a major contributor to maternal morbidity and adverse perinatal outcomes, particularly in low- and middle-income countries. Daily iron supplementation is the standard regimen; however, gastrointestinal intolerance and poor compliance have led to growing interest in intermittent dosing schedules. Evidence regarding the impact of supplementation frequency on maternal and neonatal outcomes in anaemic pregnant women remains limited.

Objectives: To compare maternal and perinatal outcomes among pregnant women with mild to moderate IDA receiving daily versus twice-weekly oral iron supplementation.

Methods: This prospective observational study was conducted at the Department of Obstetrics and Gynaecology, PGIMS Rohtak, from February 2020 to March 2021. A total of 200 pregnant women between 14–24 weeks of gestation with mild to moderate IDA were enrolled and randomized into two groups:

- Group A (n = 100): Daily supplementation with 100 mg elemental iron + 500 µg folic acid
- Group B (n = 100): Twice-weekly supplementation with two tablets (100 mg iron + 500 µg folic acid each)

Participants were monitored every 4 weeks until delivery. Maternal outcomes included gestational age at delivery, mode of delivery, obstetric complications, postpartum haemorrhage (PPH), and need for blood transfusion. Perinatal outcomes assessed were birth weight, neonatal complications, Apgar scores, and NICU admission. Statistical analysis was performed using t-test and Chi-square test, with $p < 0.05$ considered significant.

Results: Maternal baseline characteristics were similar between the two groups. Maternal complications occurred in 49% of Group A and 36% of Group B, with no statistically significant difference ($p > 0.05$). Rates of preterm labour, PROM, fetal distress, and PPH were comparable across both groups. Mode of delivery and transfusion requirements also showed no significant

variation. Perinatal outcomes—including mean birth weight (2.59 ±0.51 kg in Group A vs. 2.71 ± 0.44 kg in Group B), neonatal complications, and NICU admissions—did not differ significantly between regimens.

Conclusion: Twice-weekly iron supplementation provides maternal and perinatal outcomes comparable to daily dosing in mild to moderate IDA. Given its potential advantages in compliance and tolerability, intermittent supplementation may serve as an effective alternative in antenatal care programs.

Keywords: iron deficiency anaemia, pregnancy, intermittent supplementation, daily iron therapy, maternal outcomes, perinatal outcomes, antenatal care

INTRODUCTION

Iron deficiency anaemia (IDA) remains one of the most widespread nutritional deficiencies globally and is a major public health challenge, particularly in low- and middle-income countries. According to the World Health Organization (WHO), approximately 37% of pregnant women worldwide are anaemic, with nearly half of these cases attributable to iron deficiency [1]. Pregnant women face an increased risk because of heightened physiological demands for iron needed to support maternal erythropoiesis, fetal growth, and placental development [2]. In India, the burden of anaemia during pregnancy is especially alarming. The National Family Health Survey-5 (NFHS-5) reports that 52.2% of pregnant women are anaemic, reflecting only marginal improvement over the past decade [3]. This high prevalence translates directly into adverse maternal and perinatal health outcomes.

Maternal anaemia has been linked to multiple complications including preterm labour, postpartum haemorrhage (PPH), cardiac decompensation, and increased need for blood transfusion [4,5]. Fetal and neonatal consequences include intrauterine growth restriction (IUGR), low birth weight (LBW), stillbirth, impaired neonatal iron stores, and increased perinatal morbidity and mortality [6,7]. These risks are amplified in moderate to severe anaemia, making timely detection and effective management crucial for safe motherhood.

India has a long history of national programs aimed at combating IDA. The National Nutritional Anaemia Prophylaxis Programme (NNAPP), initiated in 1970, was later strengthened and expanded under the National Iron Plus Initiative (NIPI). Under current guidelines, pregnant women are advised to consume one tablet containing 60 mg elemental iron and 500 µg folic acid daily for at least 100 days during pregnancy [8]. While daily iron supplementation remains the standard of care, several studies have raised concerns about poor adherence due to gastrointestinal side effects, high pill burden, and perceived intolerance [9]. These challenges are particularly pronounced among pregnant women, many of whom already experience nausea, vomiting, and reduced appetite during gestation.

Given these limitations, intermittent iron supplementation—usually administered once or twice weekly—has emerged as a potential alternative. The rationale stems from both clinical and physiological observations. Intermittent dosing may reduce gastrointestinal side-effects, improve compliance, and still maintain adequate replenishment of iron stores [10]. Furthermore, intermittent dosing is supported by the “mucosal block” hypothesis: frequent daily dosing elevates hepcidin levels, which transiently suppresses intestinal iron absorption. Allowing longer intervals between doses may optimize iron bioavailability [11].

The impact of supplementation frequency on maternal and perinatal outcomes has been evaluated in several studies with varying conclusions. Some clinical trials and systematic reviews have suggested that intermittent supplementation produces comparable pregnancy outcomes related to preterm birth, LBW, and maternal morbidity as daily supplementation [12,13]. Other researchers have highlighted potential risks of less frequent dosing, particularly in populations with high prevalence of moderate anaemia or poor baseline nutritional status [14]. WHO guidelines acknowledge that intermittent iron supplementation may be considered in non-anaemic women or in regions where daily supplementation is not feasible due to adherence challenges; however,

evidence on the impact of dosing frequency among anaemic pregnant women remains limited and heterogeneous [15].

This uncertainty is especially relevant in India, where maternal anaemia is endemic and associated with significant maternal and perinatal morbidity. Despite multiple large-scale programs promoting iron supplementation, maternal outcomes such as PPH, maternal ICU admission, and blood transfusion rates remain unacceptably high among women with anaemia [5]. Similarly, neonatal outcomes such as LBW, preterm birth, and neonatal intensive care unit (NICU) admission continue to be frequently reported in this population [6,7]. Understanding whether supplementation frequency influences these outcomes is essential for optimizing antenatal protocols.

Given the persistent burden of maternal anaemia and the potential for improved compliance with intermittent regimens, the present study aims to compare maternal and perinatal outcomes among pregnant women with mild to moderate IDA receiving daily versus twice-weekly oral iron therapy. By evaluating clinical outcomes such as mode of delivery, obstetric complications, PPH, transfusion requirements, neonatal birth weight, and NICU admission, this study adds to the growing body of evidence assessing the effect of iron supplementation frequency in an anaemic pregnant population.

MATERIALS AND METHODS

Study Design and Setting: This was a prospective, randomized observational study conducted in the Department of Obstetrics and Gynaecology, Pt. B. D. Sharma Post Graduate Institute of Medical Sciences (PGIMS), Rohtak, Haryana. Data collection was carried out over February 2020 to March 2021.

Study Population: The study included pregnant women with mild to moderate iron deficiency anaemia attending the antenatal outpatient department.

Inclusion Criteria: Pregnant women who met the following criteria were eligible for inclusion

- Gestational age between 14–24 weeks
- Singleton pregnancy
- Mild to moderate iron deficiency anaemia (Hb 7–11 g/dL)
- Willingness to participate and sign informed consent

Exclusion Criteria: Exclusion applied to women with

- Known intolerance or hypersensitivity to oral iron
- Chronic systemic illness (renal, hepatic, cardiac disorders)
- Malabsorption syndromes
- Multiple pregnancy
- Intrauterine fetal demise
- Pregnancy-induced hypertension or gestational diabetes
- Untreated thyroid disorders
- Active infection or asymptomatic bacteriuria

Sample Size Calculation: The sample size was computed using the formula for comparing two means

$$N = \frac{2SD^2(Z_{\alpha/2} + Z_{\beta})^2}{d^2}$$

Using data from earlier studies (SD 0.55–0.64), with

- Zα/2 = 1.96 (5% significance level)
- Zβ = 0.842 (80% power)
- Expected difference in mean values (effect size)

The minimum calculated sample size was 65 per group. To increase power and account for dropouts, 100 women per group were included, giving a total sample size of 200 participants.

Baseline Assessment: At enrolment, all participants underwent detailed history-taking and clinical examination. Baseline investigations included:
- Complete hemogram
- Hematocrit
- Peripheral blood smear
- Blood group and Rh typing
- Viral markers (HIV, HBsAg, HCV)
- Urine routine and microscopy
- Urine culture
- Thyroid profile

All participants received Albendazole 400 mg for deworming at enrolment as per national guidelines.

Randomization and Intervention: Participants were randomly allocated into two groups using a computer-generated random sequence.

Group A (Daily Iron Group; n = 100)
- Received one tablet daily of ferrous sulfate containing
  - 100 mg elemental iron
  - 500 µg folic acid
- Provided three blister packs (10 tablets each) for 4 weeks.

Group B (Twice-Weekly Iron Group; n = 100)
- Received two tablets twice weekly (Wednesday and Sunday):
  - Each tablet contained 100 mg elemental iron + 500 µg folic acid
- Provided two blister packs (10 tablets each) for 4 weeks.
-

Both regimens were continued throughout the remaining duration of pregnancy.

Follow-Up and Monitoring: Participants were followed at 4-week intervals until delivery.
Compliance Assessment: Checked via empty blister packets & verbal confirmation of adherence.
Monitoring for Adverse Effects: Women were assessed for
- Nausea, vomiting
- Abdominal discomfort
- Diarrhoea or constipation
- Intolerance to iron preparations

Antenatal Monitoring: At each follow-up visit, a structured clinical evaluation was performed, which included
- Assessment for symptoms of anaemia
- Blood pressure measurement
- Obstetric examination
- Screening for pregnancy-related complications (e.g., preterm labour, PROM, hypertensive disorders)

Assessment of Maternal Outcomes: Maternal outcomes evaluated included
- Gestational age at delivery

- Mode of delivery (vaginal, assisted, caesarean)
- Obstetric complications (preterm labour, PROM, abruption, meconium-stained liquor, fetal distress)
- Postpartum haemorrhage (PPH)
- Need for blood transfusion
- Placental weight
- Duration of hospital stay

Assessment of Perinatal Outcomes: Perinatal outcomes included
- Birth weight of neonate
- Gestational age at birth
- Apgar scores
- Neonatal complications (respiratory distress, fetal distress, prematurity, LBW)
- NICU admission and duration of stay

Statistical Analysis: Data were collected using a structured proforma and analyzed using SPSS version 25.0.
- Quantitative variables (e.g., birth weight, placental weight, maternal hospital stay) were presented as mean ±standard deviation (SD) and compared using unpaired t-test.
- Categorical variables (e.g., mode of delivery, PPH, NICU admission) were expressed as frequency and percentage and analyzed using Chi-square test or Fisher's exact test as appropriate.
- A p-value < 0.05 was considered statistically significant.

Ethical Approval: The study protocol was reviewed and approved by the Institutional Ethics Committee, PGIMS, Rohtak. Written informed consent was obtained from all participants after providing complete information regarding the study purpose, procedures, and potential risks. Participant confidentiality was ensured, and the study adhered to the guidelines of the Declaration of Helsinki.

RESULTS

A total of 234 pregnant women consented to participate, of whom 200 met the eligibility criteria and were randomized equally into the two study groups:
Group A – Daily iron supplementation (n = 100)
Group B – Twice-weekly iron supplementation (n = 100)
Both groups were comparable in baseline demographic characteristics, parity, gestational age at enrollment, and past obstetric history. Maternal and perinatal outcomes were analyzed for all 200 women.
Parity, previous obstetric complications, and maternal weight were comparable between the two groups ($p > 0.05$). No selective clustering of high-risk history was seen.(Table 1)

Table 1. Distribution of Parity, Past Obstetric History, and Maternal Weight

Parameter	Group A (n=100)	Group B (n=100)	p-value
Primigravida	45	48	0.508
Multigravida	55	52	
Mean parity	1.91	1.80	

Table 1. Distribution of Parity, Past Obstetric History, and Maternal Weight

Significant past history (PROM, APE, PTVD, IUD, hypothyroid, BT, TB)	18%	16%	0.622
Maternal weight (kg), Mean ± SD	57.15 ± 7.06	56.20 ± 7.59	0.361

Maternal complications occurred in 49% of Group A and 36% of Group B. Although numerically lower in the twice-weekly group, the difference was not statistically significant ($p > 0.05$). Preterm labour, PROM, PPH, and fetal distress were the most frequently observed complications.(Table 2)

Table 2. Maternal Complications Observed During Current Pregnancy

Maternal Complication	**Group A (n=100)**	**Group B (n=100)**	**Total**	**p-value**
Preterm labour	13	15	28	0.684
PROM	9	5	14	
Abruptio placentae	2	1	3	
Meconium-stained liquor	6	4	10	
Fetal distress	9	6	15	
PPH	7	4	11	
Other complications	3	1	4	
Total complications	**49**	**36**	**85**	

Most women delivered at term (≥37 weeks), with similar proportions in both groups. The mode of delivery was also comparable, with vaginal births being most common. Twice-weekly iron did not negatively affect obstetric outcomes.(Table 3A, 3B)

Table 3. Maternal Delivery Outcomes A. Period of Gestation at Delivery

Gestational Age	**Group A (n=100)**	**Group B (n=100)**	**p-value**
<28 weeks	1	0	0.347
28–32 weeks	3	4	
32–34 weeks	3	2	

Table 3. Maternal Delivery Outcomes A. Period of Gestation at Delivery

34–37 weeks	19	17	
≥37 weeks	59	65	
>40 weeks	15	12	
Mean ± SD	37.79 ± 2.43	38.10 ± 2.30	0.347

Table 3: Maternal Delivery Outcomes B. Mode of Delivery

Delivery Type	**Group A**	**Group B**	**Total**	**p-value**
Term vaginal delivery	47	56	103	
Term LSCS	24	19	43	
Assisted delivery	4	3	7	0.774
Preterm vaginal delivery	22	20	42	
Preterm LSCS	4	3	7	

Birth weight distribution and incidence of neonatal complications were similar between the two groups. Although LBW and preterm birth occurred in both regimens, differences were not statistically significant.(Table 4)

Table 4. Perinatal Outcomes (Birth Weight and Neonatal Complications)

Category		**Group A (n=100)**	**Group B (n=100)**	**p-value**
Birth Weight	1.0–1.5 kg	3	3	0.087
	>1.5–<2.5 kg (LBW)	32	25	
	2.5–4 kg	65	72	
	Mean ± SD (kg)	2.59 ± 0.51	2.71 ± 0.44	0.087
Neonatal	Low birth weight	11	10	0.522

Table 4. Perinatal Outcomes (Birth Weight and Neonatal Complications)

Complications	Preterm	21	17
	Respiratory distress	0	4
	Fetal distress	10	8
	Total neonatal complications	42	39

NICU stay patterns were similar in both groups. Maternal need for blood transfusion and length of hospital stay did not differ significantly, indicating that twice-weekly supplementation did not increase postpartum morbidity.(Table 5)

Table 5: Post-Delivery Outcomes: Duration of NICU Stay, Blood Transfusion & Hospital Stay

Post-Delivery Outcome		Group A	Group B	p-value
NICU Stay Duration	≤2 days	14	10	0.756
	>2–5 days	11	11	
	>5–10 days	4	4	
	>10–15 days	0	3	
	>15–20 days	1	1	
	>20 days	1	0	
Need for Maternal Blood Transfusion	Yes	12	14	0.674
	No	88	86	
Duration of Maternal Hospital Stay	<5 days	70	77	0.651
	5–10 days	28	19	
	>10 days	2	4	
	Mean ± SD (days)	4.26 ± 2.88	4.08 ± 2.74	

DISCUSSION

Iron deficiency anaemia (IDA) in pregnancy remains a major public health concern and is strongly associated with adverse maternal and perinatal outcomes. Globally, the prevalence of anaemia in pregnancy is approximately 37% [1], while in India it remains significantly higher at over 52% according to NFHS-5.[3] Maternal anaemia has been consistently linked to complications such as preterm labour, postpartum haemorrhage (PPH), increased intra-partum interventions, and higher transfusion requirements.[4,5] For the fetus, maternal anaemia contributes to low birth weight, prematurity, intrauterine growth restriction (IUGR), and neonatal morbidity.[6] Therefore, exploring optimal iron supplementation regimens that effectively improve outcomes is a critical component of maternal health strategies.

Daily iron supplementation is the standard recommendation under national programs, including the National Iron Plus Initiative (NIPI) in India.[8] However, compliance with daily intake is often poor due to gastrointestinal adverse effects, pill burden, and misconceptions about iron tablets [9]. This has created interest in intermittent dosing schedules—once or twice weekly—as potentially more acceptable alternatives, especially in resource-limited settings. WHO acknowledges intermittent supplementation as an option for pregnant women where adherence to daily dosing is low or side-effects limit compliance [15]. Whether intermittent supplementation influences maternal and neonatal clinical outcomes differently from daily dosing remains an important question.

Maternal Outcomes

In the present study, maternal complications—including preterm labour, premature rupture of membranes (PROM), fetal distress, and postpartum haemorrhage—occurred at similar frequencies across both supplementation schedules. The absence of significant differences aligns with findings from previous trials and meta-analyses. A Cochrane review by Peña-Rosas et al. reported no clinically meaningful differences in obstetric complications between daily and intermittent regimens [10]. Similarly, studies from Indonesia, Iran, and India have shown comparable rates of preterm labour and obstetric morbidity regardless of supplementation frequency [12,13].

Preterm labour, one of the most significant consequences of maternal anaemia, occurred in 14% of the study population, matching published Indian data among moderately anaemic women [16]. Maternal anaemia contributes to preterm birth through mechanisms such as maternal hypoxia, increased infections, and activation of the HPA axis due to physiological stress [17]. The current findings suggest that when supplementation—whether daily or twice weekly—is initiated at 14–24 weeks and continued regularly, the difference in preterm birth risk is minimal.

Postpartum haemorrhage (PPH), a leading cause of maternal mortality in India, occurred in both groups without significant difference. Prior studies show that moderate anaemia increases the risk of uterine atony and PPH due to impaired myometrial contractility and reduced oxygen delivery to uterine muscles [18]. Because both groups consisted of anaemic women with similar baseline hemoglobin, comparable PPH incidence was expected. A study by Drukker et al. similarly reported that while anaemic women had higher risk of PPH, the risk did not differ significantly based on iron regimen.[5]

The need for blood transfusion—another important maternal outcome—was similar in both groups. This finding agrees with the trial by Ridwan et al. and Young et al., which found no significant differences in intrapartum or postpartum transfusion rates between daily and intermittent supplementation.[12,19] Transfusion requirements are typically driven more by severity of anaemia and intrapartum blood loss than by supplementation schedule.

Mode of delivery also did not differ significantly. Moderate anaemia is associated with increased caesarean delivery rates, partly due to associated complications such as fetal distress and maternal exhaustion [5]. However, studies comparing supplementation schedules report no influence of regimen on delivery mode, consistent with our findings.[13]

Perinatal Outcomes

Perinatal outcomes are strongly impacted by maternal iron status. Low maternal hemoglobin is associated with an increased risk of low birth weight (LBW), small-for-gestational-age (SGA) infants, neonatal hypoxia, and increased NICU admissions [6]. In this study, birth weight distribution, LBW incidence, and neonatal complications—including respiratory distress and fetal distress—did not differ significantly between the two groups.

These results parallel findings from trials in India, Iran, and Indonesia showing similar birth weights among infants born to mothers receiving daily versus intermittent iron supplementation. [12,13,20] A study by Hanie et al. found no clinically important differences in neonatal birth weight or gestational age at birth between daily and intermittent IFA regimens [20]. Likewise, Goshtasebi et al. and Mukhopadhyay et al. reported similar rates of LBW, preterm birth, and NICU admission across both regimens [21,22].

Neonatal NICU admission rates were also comparable, suggesting that the frequency of maternal iron dosing did not affect immediate neonatal adaptation. This supports evidence indicating that neonatal iron status is primarily influenced by maternal iron reserves earlier in pregnancy rather than the supplementation frequency later in gestation [6]. Since both groups initiated supplementation in the second trimester, comparable neonatal outcomes are expected.

Clinical Implications

The findings indicate that twice-weekly iron supplementation provides maternal and perinatal outcomes equivalent to daily supplementation when implemented consistently in women with mild to moderate IDA. This has several important implications:

1. Improved compliance: Intermittent dosing reduces pill burden and may be more acceptable for women experiencing pregnancy-related nausea or intolerance.
2. Resource efficiency: Using fewer tablets may reduce program costs in large-scale public health settings.
3. No compromise in clinical safety: Comparable maternal complications, delivery outcomes, neonatal birth weight, and NICU stays indicate that intermittent dosing is safe.

These findings support WHO recommendations allowing intermittent IFA as an alternative when daily dosing is not feasible or accepted [15]. In settings where compliance is poor, twice-weekly regimens could help improve overall program effectiveness without increasing risk.

CONCLUSION

This observational analysis demonstrates that maternal and perinatal outcomes among pregnant women with mild to moderate iron deficiency anaemia are comparable between daily and twice-weekly oral iron supplementation regimens. Both groups showed similar rates of obstetric complications, including preterm labour, PROM, fetal distress, and postpartum haemorrhage, with no statistically significant differences. Likewise, mode of delivery, need for maternal blood transfusion, neonatal birth weight, neonatal complications, and NICU admissions were similar across both supplementation schedules. These findings indicate that twice-weekly iron supplementation is as safe and effective as daily dosing in terms of clinical outcomes. Considering the potential advantages of improved compliance, reduced gastrointestinal side-effects, and lower pill burden, twice-weekly supplementation offers a practical and resource-efficient alternative in antenatal care. In settings with high prevalence of anaemia and variable adherence to daily IFA intake, intermittent dosing may strengthen program effectiveness without compromising maternal or neonatal safety.

Declarations

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