Thai Journal of Obstetrics and Gynaecology
September 2025, Vol. 33, No. 5, pp. 378-389

OBSTETRICS

A Comparative Study of the Efficacy of Daily and Intermittent Iron Supplementation in Pregnant Women: A randomized controlled trial

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ABSTRACT

Objectives: This study aimed to compare the effect of weekly, three times per week, and daily iron supplementation on the hemoglobin and hematocrit levels in pregnant women. A secondary objective included assessing urine iodine levels in conjunction with the adverse effects associated with the use of iron supplements in various formulations.

Materials and Methods: A randomized controlled trial was conducted using 84 pregnant women receiving antenatal care at Somdejprasangkharach 17th Hospital. Participants were randomly divided into three groups: group 1 was daily iron supplement (DIS), received one tablet of triferdine daily; group 2 was thrice weekly iron supplement (TIS), received one tablet of triferdine every other day; group 3 was weekly iron supplement (WIS), received one tablet of triferdine, ferrous fumarate, and ½ tab of folic acid once a week. To determine the efficacy, venous blood samples were collected for complete blood count and iron studies at the initial presentation and at 32–36 weeks of gestation. Any adverse effects of medication, such as abdominal pain, nausea, and vomiting, were monitored using questionnaires every 4 weeks. Medication adherence was also assessed, and participants were asked to bring their medication to each hospital visit for pill counting.

Results: The study found a statistically significant decrease in hematocrit levels among all groups in the third trimester, with 28.57%, 14.28%, and 39.28% of participants in the DIS, TIS, and WIS groups, respectively, meeting the criteria for iron deficiency anemia in the third trimester. The study found no statistically significant differences between the groups ($p = 0.064$). However, ferritin levels decreased significantly and differently between the groups ($p = 0.033$), with the lowest values observed in the WIS group. The prevalence of low serum ferritin was 46.4%, 64.3%, and 71.4% in the DIS, TIS, and WIS groups, respectively. There were no significant differences in side effects among groups.

Conclusion: The results of this study indicated a reduction in hematocrit levels across all study groups throughout the third trimester. Although comparisons between groups revealed no significant differences in hematocrit and hemoglobin level, the WIS group had the highest incidence of iron deficiency anemia. Based on the study results, we concluded that the TIS group demonstrated the highest efficacy in preventing iron deficiency anemia during pregnancy

Keywords: iron supplement, pregnancy, iron deficiency anemia, antenatal care, hemoglobin.

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Received: 13 February 2025, **Revised:** 20 August 2025, **Accepted:** 22 August 2025

การศึกษาเปรียบเทียบประสิทธิภาพของการเสริมธาตุเหล็กแบบทุกวันและแบบเป็นระยะในหญิงตั้งครรภ์: การทดลองแบบสุ่มที่มีกลุ่มควบคุม

พรศักดิ์ ถิรธนบูรณ์

บทคัดย่อ

วัตถุประสงค์: *เพื่อเปรียบเทียบผลของการให้ยาเสริมธาตุเหล็กแบบให้สัปดาห์ละครั้ง แบบให้ 3 ครั้งต่อสัปดาห์ และแบบให้ทุกวันต่อระดับฮีโมโกลบินและระดับฮีมาโตคริตในสตรีตั้งครรภ์ และมีวัตถุประสงค์รองเพื่อศึกษาปริมาณไอโอดีนในปัสสาวะและอาการไม่พึงประสงค์ของการให้ยาแต่ละแบบ*

วัสดุและวิธีการ: *เป็นการศึกษาทดลองแบบสุ่มที่มีกลุ่มควบคุม ในผู้หญิงตั้งครรภ์ที่มาเข้ารับการฝากครรภ์ที่โรงพยาบาลสมเด็จพระสังฆราชองค์ที่ 17 จำนวน 84 ราย โดยอาสาสมัครถูกแบ่งออกเป็น 3 กลุ่มแบบสุ่ม ได้แก่ กลุ่มที่ได้รับยากลุ่มที่ 1 daily iron supplement (DIS) ได้รับ triferdine รับประทานวันละ 1 เม็ด กลุ่มที่ 2 thrice weekly iron supplement (TIS) ได้รับ triferdine รับประทาน 1 เม็ด วันเว้นวัน และกลุ่มที่ 3 weekly iron supplement (WIS) ได้รับ triferdine รับประทาน 1 เม็ด และ ferrous fumarate 1 เม็ด และ folic acid ครึ่งเม็ด สัปดาห์ละ 1 ครั้ง ประเมินประสิทธิภาพของการได้รับยาโดยเจาะเลือดตรวจระดับ CBC และ iron study ที่แรกรับและอีกครั้ง ที่อายุครรภ์ 32-36 สัปดาห์ จากนั้นติดตามสอบถามอาการไม่พึงประสงค์ของการใช้ยา เช่น อาการปวดท้อง คลื่นไส้ อาเจียน เป็นต้น โดยใช้แบบสอบถาม ทุก ๆ 4 สัปดาห์ รวมถึงการสอบถามความสม่ำเสมอของการรับประทานยา และให้นำยามาด้วยทุกครั้งเมื่อมาที่โรงพยาบาลเพื่อนับเม็ดยา*

ผลการศึกษา: *จากผลการศึกษาพบว่าระดับฮีมาโตคริตลดลงอย่างมีนัยสำคัญทางสถิติในทุกกลุ่มตัวอย่างที่ไตรมาสที่ 3 และเข้าเกณฑ์ภาวะโลหิตจางจากการขาดธาตุเหล็กในไตรมาสที่ 3 ร้อยละ 28.57, 14.28 และ 39.28 ในกลุ่ม DIS, TIS และ WIS ตามลำดับ ไม่พบมีความแตกต่างกันอย่างมีนัยสำคัญระหว่างกลุ่ม ($p = 0.064$) ในขณะที่ระดับ ferritin มีค่าลดลงแตกต่างกันอย่างมีนัยสำคัญระหว่างกลุ่ม ($p = 0.033$) โดยพบค่าน้อยที่สุดในกลุ่มตัวอย่างกลุ่ม WIS และพบภาวะ serum ferritin ต่ำ คิดเป็น ร้อยละ 46.4, 64.3 และ ร้อยละ 71.4 ในกลุ่ม DIS, TIS และ WIS ตามลำดับ ไม่พบอาการข้างเคียง*

สรุป: *จากผลการศึกษาพบว่าระดับฮีมาโตคริตลดลงในไตรมาสที่ 3 ทั้ง 3 กลุ่ม ถึงแม้ว่าไม่พบความแตกต่างของระดับฮีมาโตคริตและฮีโมโกลบินระหว่างกลุ่มอย่างมีนัยสำคัญ แต่พบความชุกของภาวะซีดจากการขาดเหล็กในกลุ่มที่ได้รับยาหนึ่งครั้งต่อสัปดาห์ ผลการศึกษาสรุปได้ว่าการได้รับยาแบบ TIS มีประสิทธิภาพสูงที่สุดในการป้องกันภาวะโลหิตจางจากการขาดธาตุเหล็กในหญิงตั้งครรภ์*

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Introduction

Anemia is a prevalent illness among pregnant women that can impact the health of both the mother and the fetus[1]. It may result from various circumstances, including starvation, illness, and genetic disorders[2]. Several micronutrients, including iron, folate, vitamins A, B12, and C[3], contribute to anemia, with iron deficiency being the most prevalent cause.

The prevalence among pregnant women worldwide ranges between 29.0-42.7%[4]. In Southeast Asia, the prevalence is as high as 48%. In Thailand, approximately 6.92 – 30% of pregnant women have anemia at first antenatal care (ANC)[5–7], Thongperm et al[8] reported that the prevalence of anemia among pregnant women in Trang province was found to be 17.2% at the first visit, which increased to 22.5% and 50% in the second and third trimesters, respectively. The predominant reasons were attributed to thalassemia, with only 5% resulting from iron deficiency. According to statistical data compiled from the record at Somdejprasangkharach 17th Hospital, the prevalence of anemia among pregnant women was around 23.6%, 17.58%, and 19.51% in 2020, 2021 and 2022, respectively.

Iron deficiency is the most important cause of anemia during pregnancy, with an incidence of 18-19% in the United States. Pregnancy requires iron to meet the physiological demands of the fetus and promote blood flow as well as tissue development in the body[9,10]. The maternal demand for iron grows from 1 to 2.5 mg per day during the first trimester, reaching 6.5 mg per day in the third trimester. The body necessitates approximately 1 gram of iron throughout pregnancy, with 360 mg allocated for the fetus and placenta, and 450 mg designated for the synthesis of red blood cells in the mother. Of the remaining 240 mg, it is excreted by feces, urine, and perspiration[11]. During pregnancy, untreated iron deficiency is associated with an increased risk of iron deficiency anemia, placental hypertrophy, and maternal hypothyroidism[12]. If serum ferritin is below 15 µg/L, it signifies iron deficiency, and it is classified as iron deficiency anemia[13] when accompanied by hemoglobin levels under 11 g/dL.

The World Health Organization (WHO) characterizes pregnant women as having anemia when their Hb levels are less than 11 g/dl in the first and third trimesters, and Hb is less than 10.5 g/dl in the second trimester[14,15]. In 2012, the WHO recommended daily oral iron and folic acid supplementation as a crucial component of prenatal care[16]. Subsequently, the WHO guidelines in 2016 suggested a weekly iron supplementation regimen of 120 mg combined with 2,800 micrograms (2.8 mg) of folic acid for pregnant women when daily iron intake is impractical. This recommendation acknowledges the intestinal mucosa's rapid turnover, occurring every 5 to 6 days. The rationale for weekly administration is to optimize intestinal iron absorption and minimize the potential for free radical formation associated with excessive iron accumulation within the intestinal tract[17]. Moreover, prior research indicated that administering iron supplements weekly yielded no distinct effects on anemia in near-term pregnant women, low birth weight infants, and premature births compared to daily administration. Additionally, side effects from iron supplementation were less frequent, and pregnant women were more compliant with continuous intake[18,19]. Following the iron supplement, hepcidin, a liver-cell-derived protein that is crucial to regulating iron metabolism, would be elevated. This elevation inhibits intestinal iron absorption within 24 hours. Previous research suggested that iron supplementation exceeding 60 mg promoted intestinal iron absorption if administered with a 48-hour interval[20], contrary to the World Health Organization's recommendation of weekly administration.

The study by Bouzari et al[21] revealed that daily iron supplementation and weekly iron supplementation were equally effective in preventing anemia among pregnant women. However, the study provided only 50 milligrams of iron in the group that received it once a day and every other day, allowing 100 milligrams of iron in the form of 1 time per week, with 60 milligrams of iron, which is different from the 60 milligrams of iron supplement provided in Thailand. In addition, the

previous study has indicated that iron supplementation in non-anemic pregnant women leads to elevated blood iron levels and is associated with an increased risk of preterm birth, low birth weight, and gestational diabetes mellitus[22, 23].

Goonewardene et al[24] likewise reported that a group receiving iron supplements once weekly and thrice weekly had a greater risk of iron deficiency compared to a group receiving daily supplements, with no variation in side effects from the medications. Thus, it is advisable to consume iron supplements daily, as this is more efficacious in preventing anemia.

The primary objective of this study was to examine the comparative efficacy of intermittent iron supplementation administered once a week, thrice a week, and daily.

To evaluate the efficacy, blood samples were collected for complete blood count and iron studies at the initial presentation and at 32-36 weeks of gestation. As commercially available iron supplements are fortified with iodine, different supplementations may have variable effects on maternal iodine levels. Consequently, the secondary objective of this study was to assess urine iodine levels in conjunction with adverse effects, such as nausea, abdominal pain or constipation, to determine the most appropriate iron supplementation for pregnant women.

Materials and Methods

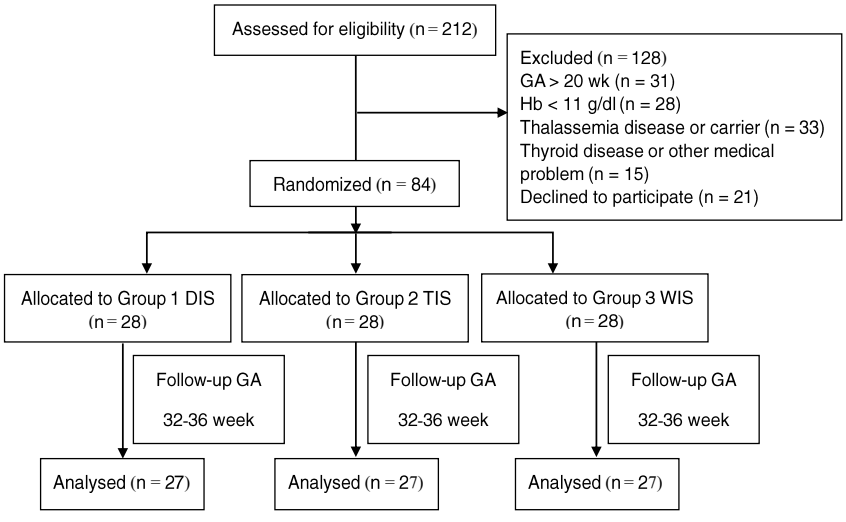
This open-label randomized controlled study was conducted among pregnant women seeking antenatal care at Somdejprasangkharach 17th Hospital from April 2023 to March 2024. The study was approved by the Human Research Ethics Committee of the Public Health Office, Suphan Buri Province. The trial was prospectively registered in the Thai Clinical Trials Registry (TCTR20230310002) on 10 March 2023. The pregnancies of those who had a body mass index (BMI) ≥ 18.5 kg/m^2, were aged between 18 and 50 years, had a gestational age of less than 20 weeks, and had hemoglobin (Hb) ≥ 11 g/dl or hematocrit (Hct) ≥ 33%, no history of iron deficiency anemia or taking iron supplements were included. Pregnant women were excluded if they had a history of diseases related to the blood system and iron metabolism, anemia, chronic diseases affecting iron absorption, malabsorption, bariatric surgery, or complications during pregnancy such as preterm labor, preterm premature rupture of membranes (PPROM), and infections.

The participants who met the inclusion criteria were randomly assigned to one of three groups, including group 1, daily iron supplement (DIS), group 2, thrice a week iron supplement (TIS), and group 3, weekly iron supplement (WIS)) using a computer-generated block randomization method. Random numbers were assigned in opaque envelopes after the participants provided written informed consent.

All participants were asked about demographic information, including age, chronic illnesses, and obstetric history. Baseline venous blood specimens were collected for complete blood count (CBC), iron studies, and C-reactive protein (CRP). Urine samples were obtained for iodine assessment. Urine iodine concentrations were measured using the Sandell-Kolthoff method. Results were expressed in µg/L, with intra-assay and inter-assay coefficients of variation of 3-5% and 6-12%, respectively. Afterward, the participants in group 1 (DIS) received daily triferdine (potassium iodide 196 mcg, ferrous fumarate 185 mg, and folic acid 400 mcg). Group 2 (TIS) received triferdine every other day, while group 3 (WIS) received weekly triferdine plus ferrous fumarate (200 mg), and a half tablet of folic acid (5 mg). In the WIS group, additional ferrous supplementation was required. Since triferdine contains iodine, ferrous fumarate 200 mg was selected as the supplementary iron source to avoid excessive iodine exposure in participants. Treatment initiation occurred following confirmation of inclusion and exclusion criteria and patient consent to participate in the study. Treatment was discontinued under two conditions: 1) anemia was detected in the second blood assessment, or 2) when the second blood results were normal, medication was continued until delivery. Follow-up blood and urine samples were collected at 32 to 36 weeks of gestation. All participants were provided with medications that were placed in

plastic bags with drug administration labeled by hospital pharmacists to increase patient compliance and prevent dosage errors.

Participants were instructed to bring all medication containers to each scheduled antenatal visit (every 4 weeks). At each visit, pill counts were conducted to calculate the number of tablets consumed and the remaining quantity to assess medication adherence. Side effects of iron supplementation, such as abdominal pain, nausea, and vomiting, were recorded by a questionnaire administered every four weeks, which also evaluated adherence to the supplementation schedule. Additionally, participants were systematically questioned about any abnormal bleeding symptoms at every 4 weeks, as we would like to detect if there was any other cause of anemia during the study period. Information regarding birth history, including delivery method, gestational age, and neonatal weight, was collected. The flow of the participants is summarized in Fig. 1.



DIS: Daily iron supplement, TIS: Thrice a week iron supplement, WIS: Weekly iron supplement

Fig. 1. Study flow diagram.

The sample size was calculated for a three-group by analysis of variance (ANOVA) design[25] using the following parameters: $\alpha = 0.05$, $\beta = 0.05$, and effect size = 0.5330[21]. This determined a minimum of 22 participants per group. Adjusting for an expected 20% attrition rate, the final sample size was calculated as 28 participants per group (n = 22/0.8 = 28). Data analysis was conducted on a computer using SPSS version 27. Descriptive data were analyzed for both qualitative and quantitative variables. ANOVA and Bonferroni's post hoc test were employed to evaluate continuous variables, both within and between groups, before and after supplementation.

Results

A total of 84 pregnant women participated, and they were randomly assigned into 3 groups of 28 volunteers each. Table 1 presents the general information of participants in each group. No statistically significant variations were seen in terms of maternal age, gestational age at initial visit, body mass index, hemoglobin concentration, hematocrit, mean corpuscular volume, serum iron, serum ferritin, transferrin saturation, total iron binding capacity (TIBC), and CRP among the groups. Nonetheless, a statistically significant disparity in urine iodine levels was observed, with group 2 exhibiting markedly greater levels than the other groups (p = 0.01), and

no anemia was detected upon initial admission.

Upon follow-up at gestational ages of 32 to 36 weeks, no significant differences were observed in the levels of hemoglobin, hematocrit, MCV, serum iron, transferrin saturation, total iron binding capacity, urine iodine, and CRP among the groups. However, a statistically significant disparity in ferritin levels was observed between the groups. Post-hoc analysis utilizing the Bonferroni technique revealed a statistically significant difference between group 1 DIS and group 3 WIS (p = 0.028), as illustrated in Table 2.

Table 1. Participant's demographic data.

	DIS (n = 28)	TIS (n = 28)	WIS (n = 28)	p value
Age (years)	24.07 ± 6.06	24.82 ± 5.23	22.71 ± 3.83	0.301
GA at first visit (weeks)	14.04 ± 2.72	13.50 ± 2.50	13.96 ± 2.55	0.703
BMI (kg/m^2)	22.58 ± 6.56	24.53 ± 5.81	23.63 ± 5.89	0.491
Hemoglobin (g/dl)	12.57 ± 0.85	12.59 ± 0.84	12.50 ± 0.96	0.919
Hematocrit (%)	38.06 ± 2.09	38.04 ± 2.46	37.72 ± 2.69	0.840
MCV (fl)	85.26 ± 4.65	83.93 ± 5.80	84.55 ± 5.55	0.650
Serum iron (µg/dl)	78.54 ± 31.38	80.45 ± 31.75	81.32 ± 23.97	0.936
Serum ferritin (ng/ml)	108.832 ± 100.17	100.68 ± 78.46	79.89 ± 59.94	0.393
TIBC(µg/dl)	315.29 ± 50.67	305.11 ± 72.13	299.86 ± 91.36	0.726
Transferin saturation (%)	25.79 ± 11.40	26.29 ± 11.80	25.95 ± 11.00	0.981
CRP (mg/l)	12.15 ± 16.86	8.97 ± 9.87	5.10 ± 3.33	0.076
Duration of supplement (days)	116 ± 9.89	132.5 ± 10.60	126 ± 19.79	0.853
Urine iodine (µg/L)	165.03 ± 86.10	268.43 ± 186.45	158.85 ± 82.13	0.002*

DIS: daily iron supplement, TIS: thrice weekly iron supplement, WIS: weekly iron supplement, GA: gestational age, BMI: body mass index, MCV: mean corpuscular volume, TIBC: total iron binding capacity, CRP: C-reactive protein
Data expressed as mean ± standard deviation.
*statistical significance at $p < 0.05$ when analyzed with ANOVA.

Table 2. Comparative data of the results of the second blood test between groups.

	DIS (n = 27)	TIS (n = 27)	WIS (n = 27)	p value
Hemoglobin (g/dl)	12.72 ± 5. 11	12.58 ± 3.67	11.32 ± 0.92	0.306
Hematocrit (%)	35.53 ± 2.28	35.90 ± 2.92	34.30 ± 2.52	0.064
MCV (fl)	84.19 ± 15.43	85.62 ± 5. 45	84.77 ± 5.36	0.865
Serum iron (µg/dl)	91.37 ± 47.08	85.07 ± 50.22	66.89 ± 68.82	0.256
Serum ferritin (ng/ml)	35.95 ± 22.15	29.70 ± 21.94	21.71 ± 13.60	0.033*
TIBC(µg/dl)	438.41 ± 55.50	451. 54 ± 61.02	469.89 ± 50.24	0.121
Transferrin saturation (%)	21.30 ± 11.52	18.93 ± 10.55	14.48 ± 15.22	0.136
Urine iodine (µg/L)	204.17 ± 213.19	180.52 ± 131. 71	173.70 ± 118.36	0.763
CRP (mg/l)	4.81 ± 5.31	7.58 ± 10.18	5.80 ± 5.69	0.380

DIS: daily iron supplement, TIS: thrice weekly iron supplement, WIS: weekly iron supplement, GA: gestational age, BMI: body mass index, MCV: mean corpuscular volume, TIBC: total iron binding capacity, CRP: C-reactive protein
Data expressed as mean ± standard deviation.
* statistical significance at $p < 0.05$ when analyzed with ANOVA statistics.

The follow-up blood test (during the third trimester of pregnancy) revealed iron deficiency anemia (Hb < 11) in 8 (28.57%), 4 (14.28%), and 11 (39.28%) subjects in the DIS, TIS, and WIS groups, respectively. Despite its higher prevalence in the WIS group compared to the other groups, the difference was not statistically significant (p = 0.109). The prevalence of low serum ferritin levels (< 30 µg/L) in the DIS, TIS, and WIS groups was 46.4%, 64.3%, and 71.4%, respectively. Despite its higher prevalence in the WIS group compared to the other groups, the difference was not statistically significant (p = 0.143).

No significant difference in urinary iodine concentrations was observed between groups at the second assessment.

Significant decreases in hematocrit and serum ferritin accompanied by increased TIBC were observed uniformly across treatment groups post-intervention, with no detectable changes in hemoglobin, MCV, or serum iron concentrations. (Table 3)

Table 3. Mean difference of pre and post blood test within group.

	Group		mean ± SD	mean difference ± SD	95%CI		p value
Hematocrit (%)	DIS	pre	38.06 ± 2.09	2.48 ± 2.17	1.62	3.34	< 0.001*
		post	35.53 ± 2.28				
	TIS	pre	38.04 ± 2.46	2.14 ± 3.12	0.93	3.35	0.001*
		post	35.90 ± 2.92				
	WIS	pre	37.72 ± 2.69	3.51 ± 1.98	2.73	4.29	< 0.001*
		post	34.30 ± 2.52				
Hemoglobin (g/dl)	DIS	pre	12.57 ± 0.85	-0.17 ± 5.03	-2.16	1.81	0.856
		post	12.72 ± 5. 11				
	TIS	pre	12.59 ± 0.84	0.01 ± 3.72	-1.42	1.45	0.984
		post	12.58 ± 3.67				
	WIS	pre	12.50 ± 0.96	1.22 ± 0.67	0.96	1.49	< 0.001*
		post	11.32 ± 0.92				
MCV (fl)	DIS	pre	85.26 ± 4.65	0.98 ± 15.06	-4.97	6.93	0.738
		post	84.19 ± 15.43				
	TIS	pre	83.93 ± 5.80	-1.68 ± 2.93	-2.82	-0.54	0.005*
		post	85.62 ± 5. 45				
	WIS	pre	84.55 ± 5.55	0.48 ± 3.63	-0.95	1.92	0.495
		post	84.77 ± 5.36				
Serum iron (µg/dl)	DIS	pre	78.54 ± 31.38	-12.07 ± 48.68	-31.33	7.18	0.209
		post	91.37 ± 47.08				
	TIS	pre	80.45 ± 31.75	-4.60 ± 50.90	-24.34	15.13	0.636
		post	85.07 ± 50.22				
	WIS	pre	81.32 ± 23.97	15.22 ± 63.06	-9.72	40.17	0.221
		post	66.89 ± 68.82				
Serum ferritin (ng/ml)	DIS	pre	108.832 ± 100.17	56.80 ± 43.56	39.56	74.03	< 0.001*
		post	35.95 ± 22.15				
	TIS	pre	100.68 ± 78.46	70.97 ± 66.86	45.05	96.90	< 0.001*
		post	29.70 ± 21.94				
	WIS	pre	79.89 ± 59.94	55.00 ± 51.81	34.50	75.50	< 0.001*
		post	21.71 ± 13.60				
TIBC (µg/dl)	DIS	pre	315.29 ± 50.67	-120.70 ± 50.32	-140.61	-100.79	< 0.001*
		post	438.41 ± 55.50				
	TIS	pre	305.11 ± 72.13	-146.42 ± 70.56	-173.79	-119.06	<0.001*
		post	451. 54 ± 61.02				
	WIS	pre	299.86 ± 91.36	-171.95 ± 99.05	-211.14	-132.76	<0.001*
		post	469.89 ± 50.24				
Transferrin saturation (%)	DIS	pre	25.79 ± 11.40	4.59 ± 12.46	-0.33	9.52	0.067
		post	21.30 ± 11.52				
	TIS	pre	26.29 ± 11.80	7.35 ± 13.81	1.99	12.71	0.009*
		post	18.93 ± 10.55				
	WIS	pre	25.95 ± 11.00	11.62 ± 15.02	5.68	17.57	<0.001*
		post	14.48 ± 15.22				

Table 3. Mean difference of pre and post blood test within group. (Cont.)

	Group		mean ± SD	mean difference ± SD	95%CI		p value
Urine Iodine (µg/L)	DIS	pre	165.03 ± 86.10	-38.93 ± 224.70	-127.82	49.95	0.376
		post	204.17 ± 213.19				
	TIS	pre	268.43 ± 186.45	87.91 ± 190.26	14.13	161.68	0.021*
		post	180.52 ± 131. 71				
	WIS	pre	158.85 ± 82.13	-15.49 ±129.47	-66.71	35.72	0.540
		post	173.70 ± 118.36				
CRP (mg/l)	DIS	pre	12.15 ± 16.86	7.33 ± 15.38	1.25	13.42	0.020*
		post	4.81 ± 5.31				
	TIS	pre	8.97 ± 9.87	1.39 ± 5.56	-0.76	3.54	0.197
		post	7.58 ± 10.18				
	WIS	pre	5.10 ± 3.33	-0.86 ± 5.43	-3.01	1.28	0.415
		post	5.80 ± 5.69				

DIS: daily iron supplement, TIS: thrice weekly iron supplement, WIS: weekly iron supplement, GA: gestational age, BMI: body mass index, MCV: mean corpuscular volume, TIBC: total iron binding capacity, CRP: C-reactive protein, SD: standard deviation, CI: confidence interval
* statistical significance at $p < 0.05$ when analyzed with paired t-test

Between-group analysis revealed no statistically significant differences in the incidence of adverse gastrointestinal events, including nausea, vomiting, constipation, diarrhea, and flatulence. Similarly, no significant differences were observed in the frequency of taste disturbances between treatment groups.

There was no evidence of preterm labor or perinatal death in any of the groups. All infants had normal Apgar scores. No statistically significant differences were observed between the groups concerning hematocrit levels, thyroid-stimulating hormone (TSH) levels, or birth weight. (Table 4)

Table 4. Neonatal outcomes.

	Group 1 DIS (n = 20)	Group 2 TIS (n = 23)	Group 3WIS (n = 17)	p value
Hematocrit (%)	53.36 ± 6.97	51.67 ± 5.03	50.35 ± 4.64	0.276
BW < 2,500 g	3 (15%)	3 (13.4%)	1 (5.88%)	0.780
Birthweight	3043.50 ± 395.35	2982.17 ± 500.30	2995.29 ± 389.83	0.894
TSH levels	3.14 ± 2.31	2.49 ± 2.28	3.27 ± 3.26	0.586

DIS: daily iron supplement, TIS: thrice weekly iron supplement, WIS: weekly iron supplement, BW: birth weight, TSH: thyroid-stimulating hormone

Discussion

The results of the study indicated a significant reduction in hemoglobin levels across all sample groups throughout the third trimester, with incidences of iron deficiency anemia recorded at 28.57%, 14.28%, and 39.28% in groups 1 DIS, 2 TIS, and 3 WIS, respectively. No substantial difference existed between the groups. Simultaneously, the ferritin levels exhibited a substantial decline throughout the groups, with group 3 WIS recording the lowest value and ferritin levels at 46.4%, 64.3%, and 71.4% in groups 1 DIS, 2 TIS, and 3 WIS, respectively.

Anemia is a prevalent condition affecting from 19.3% to 57.4% of the population[6,19,26]. The prevalence seen in this study was comparable. This occurs because, during pregnancy, the quantity of red blood cells rises by 25%, while the plasma volume expands by 50%. The altered proportion led to a reduction in hemoglobin levels, causing anemia accompanied by iron depletion during pregnancy. Inadequate iron intake increased the risk of anemia[12].

Anemia is associated with several maternal and

newborn symptoms, including maternal fatique, early birth, low birthweight, postpartum hemorrhage, infant anemia, and potential impacts on brain function[5, 27–31]. Thus, anemia monitoring is essential for pregnant women. The hemoglobin level alone is insufficient to determine the quantity of stored iron. Consequently, ferritin levels provide a more precise and sensitive evaluation[32, 33]. The sensitivity of ferritin levels is 89%, whereas that of hemoglobin levels is 29%. Utilizing a cut-off threshold of < 30 ng/ml, the sensitivity and specificity for the diagnosis of iron deficiency anemia are 92% and 98%, respectively. The study revealed that the proportion of individuals with low ferritin levels exceeded that of those with low hemoglobin levels. The disparity in ferritin levels across the three experimental groups indicates that assessing ferritin levels may serve as a superior screening method for iron deficiency anemia compared to evaluating hemoglobin levels alone. Nonetheless, inflammation in the body may influence ferritin levels. Therefore, data should be taken cautiously in the presence of inflammation.

This study revealed a significant decrease in the levels of hematocrit and serum ferritin with an increase in the TIBC level in all three groups despite unchanged hemoglobin levels, indicating that iron deficiency anemia is still present after iron supplementation. While serum iron levels were maintained because of active supplementation, the presence of iron deficiency markers suggests inadequate therapeutic response. This suboptimal outcome is probably due to two factors: the physiological plasma volume expansion during pregnancy and the possibility of iron malabsorption or lower bioavailability, which limits utilization[34]. These findings aligned with previous studies. Srimaneesiri et al[35] conducted a study to evaluate the effect of vitamin C for daily iron supplementation in pregnant women with high-risk anemia. They found that hemoglobin and hematocrit levels decreased at the 8-week follow-up, which might have been due to physiological plasma volume expansion, inadequate nutrition, or insufficient iron supplementation. In the WIS group, a combination of Triferdine and ferrous fumarate was used to achieve 120 mg of elemental iron while avoiding excessive iodine intake. However, despite this approach, the WIS group demonstrated markedly reduced ferritin levels compared to the other two groups suggesting that daily or alternate-day iron supplementation diminishes the prevalence of anemia. Nevertheless, an examination of the ferritin levels revealed that only the cohort receiving daily iron supplements exhibited an average ferritin level within the normal range. This finding aligned with the research conducted by Ridwan et al[36], which indicated that the group administering iron daily had elevated ferritin levels compared to those receiving it weekly. According to Bumrungpert et al[37], which compared the administration of 120 mg ferrous bisglycinate and folinic acid with 200 mg ferrous fumarate once daily in pregnant women, the findings revealed that although serum iron levels increased in both groups, the group receiving ferrous bisglycinate and folinic acid demonstrated higher serum iron concentrations despite receiving a lower iron dosage. This phenomenon can be attributed to the co-administration of iron with folic acid, which plays important roles in supporting the absorption and metabolism of iron, hemoglobin, and erythrocytes. In contrast, a study by Sadaf et al[38] concluded that weekly supplementation provided an equivalent protective effect to daily intake. In the study by Sadaf et al, the cohort that ingested iron weekly received 130 mg, surpassing the amount in this study. The measurement was evaluated based on Hb and Hct values rather than ferritin values.

The study by Bouzari et al[21], which examined iron administration patterns to prevent anemia in pregnant women, revealed no differences in hemoglobin and ferritin levels across the three groups, despite all groups exhibiting decreased ferritin levels. This may have resulted from variations in ethnicity and nutritional status, which were not evaluated in this study. The study by Nisar et al[40] demonstrated that both daily and weekly iron supplementation could elevate blood concentration and ferritin levels in both groups. Both participants acquired knowledge

regarding the significance of iron supplementation and an appropriate diet, which may account for the increase in hemoglobin and ferritin levels in both groups.

The research conducted by Abdelgawad et al[39] indicated that administering iron once weekly could aid in the prevention of anemia. However, the participants were administered 200 mg of iron weekly, exceeding the 120 mg provided in this study. The study was constrained by the small sample size in each group, potentially resulting in a lack of statistically meaningful differences. Nevertheless, it was determined that weekly iron supplementation was unlikely to adequately moderate the prevalence of anemia.

Furthermore, Bhatla et al[40] demonstrated that pregnant women receiving daily iron supplementation showed significantly elevated lipid peroxidation levels compared to controls. This increased oxidative stress and subsequent membrane damage from lipid peroxidation has been implicated in the development of serious pregnancy complications, including preeclampsia and intrauterine growth restriction. These findings suggest that excessive iron supplementation during pregnancy may potentially compromise both maternal and fetal health outcomes. Adequate iodine intake is crucial for thyroid hormone synthesis and fetal neurodevelopment, yet achieving optimal iodine status remains challenging. In this study, the TIS group showed significantly higher baseline urinary iodine levels compared to other groups, but no significant between-group differences were observed at the second assessment. Additionally, infant thyroid function parameters showed no significant differences between groups. These findings suggest that iron supplementation does not substantially disrupt iodine homeostasis in pregnant women. However, larger studies with extended follow-up are needed to definitively establish the safety of iodine-containing iron supplements during pregnancy This open label randomized controlled trial aimed to evaluate various iron supplement formulations with comprehensive long-term follow-up through delivery, providing significant insights into intermittent iron supplementation in the Thai population. However, limitations should be addressed. First, the sample size in this study may have been insufficient to identify clinically significant differences. Second, nutritional factors were not evaluated, which could have influenced iron absorption. Finally, the open-label design of this study constitutes a limitation, as the lack of blinding may have introduced observer and participant bias. Further research should investigate other dosage regimens or combinations with other nutrients that may improve iron absorption and efficacy with larger sample sizes, conducting thorough nutritional assessments.

Conclusion

The results of this study indicated a reduction in hematocrit levels across all study groups throughout the third trimester. Although between-group comparisons revealed no significant differences, the WIS group was found to have the highest incidence of iron deficiency anemia. Based on the study results, we concluded that the TIS group demonstrated the highest efficacy in preventing iron deficiency anemia during pregnancy.

Acknowledgement

The authors gratefully acknowledge the prenatal care and labor room staff for their assistance with data collection, and Somdejprasangkharach 17th Hospital for providing research funding.

Potential conflicts of interest

The author declares no conflicts of interest.

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