

# ความสม่ำเสมอในการรับประทานยาเม็ดเสริมธาตุเหล็กในระหว่างตั้งครรภ์

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## Compliance of Iron Supplementation During Pregnancy

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**หลักการและวัตถุประสงค์:** เพื่อประเมินความสม่ำเสมอในการรับประทานยาเม็ดเสริมธาตุเหล็ก และระดับฮีโมโกลบินในหญิงตั้งครรภ์ไตรมาสที่ 2 และเมื่อครรภ์ครบกำหนด อันจะเป็นประโยชน์ในการพิจารณาเสริมธาตุเหล็กให้เหมาะสมต่อไป

**วิธีการศึกษา:** สตรีตั้งครรภ์ครบกำหนดมาคลอดที่โรงพยาบาลศรีนครินทร์ โดยไม่มีภาวะซีดเมื่อมาฝากครรภ์ครั้งแรก ที่ได้รับยาเม็ดเสริมธาตุเหล็กก่อนอายุครรภ์ 20 สัปดาห์ จะได้รับการสัมภาษณ์ถึงความสม่ำเสมอและผลข้างเคียงของยาเม็ดเสริมธาตุเหล็ก ซึ่งความสม่ำเสมอแบ่งออกเป็น 4 กลุ่ม คือ กลุ่มที่รับประทานมากกว่าร้อยละ 80 (6-7 เม็ดต่อสัปดาห์), ร้อยละ 50-80 (3-5 เม็ดต่อสัปดาห์), ร้อยละ 25-50 (2 เม็ดต่อสัปดาห์) และน้อยกว่าร้อยละ 25 (0-1 เม็ดต่อสัปดาห์) ส่วนฮีโมโกลบินในไตรมาสที่ 2 และเมื่อครรภ์ครบกำหนดได้ข้อมูลจากเวชระเบียน

**ผลการศึกษา:** อาสาสมัคร 350 ราย พบว่า กว่าร้อยละ 80 มีความสม่ำเสมอในการรับประทานยาเม็ดเสริมธาตุเหล็ก 6-7 เม็ดต่อสัปดาห์ มีผลข้างเคียงร้อยละ 10.5, 12.1 และ 66.7 ในกลุ่มที่มีความสม่ำเสมอในการรับประทานมากกว่าร้อยละ 80, ร้อยละ 50-80 และน้อยกว่าร้อยละ 25 ตามลำดับ ผลข้างเคียงที่พบบ่อยคือ คลื่นไส้และท้องผูก

**สรุป:** สตรีตั้งครรภ์มากกว่าร้อยละ 80 รับประทานยาเม็ดเสริมธาตุเหล็ก 6-7 เม็ดต่อสัปดาห์

**คำสำคัญ:** การเสริมธาตุเหล็ก; ความสม่ำเสมอ; ผลข้างเคียง; ตั้งครรภ์

**Background and objectives:** This study aimed to determine the compliance rate of iron supplementation and the hemoglobin concentration in second trimester and at term of pregnant women to take into consideration for the optimal practice.

**Methods:** The study conducted among term pregnant women admission to the hospital for delivery who had non-anemic status at the initial visit for antenatal care, received daily iron supplementation before 20 weeks of gestation. They were interviewed to obtain the personal data, daily taking the supplemented tablet and side-effects. The compliance rate categorized as >80%, >50-80%, 25-50%, and < 25% according to the women's response that they took daily tablet of 6-7, 3-5, 2, and 0-1 day(s) in one week, respectively. The laboratory results of hemoglobin level were retrieved from their medical records.

**Results:** Among 350 participants had the compliance rate of >80%. The common side-effects were nausea and constipation. The side-effect rates were 10.5%, 12.1%, 66.7% in >80%, >50-80%, <25% compliance groups, respectively. While hemoglobin concentrations above 13 gm/dl, which defined as high concentrated hemoglobin, revealed 12% during second trimester, and up to 30% at term in high compliance group.

**Conclusions:** The pregnant women had compliance rate greater than 80% of taking iron supplementation 6-7 tablet/week.

**Keywords:** iron supplementation; compliance; side-effects, pregnancy

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## Introduction

Worldwide prevalence of anemia among pregnant women was 41.8% and iron deficiency anemia was the most common cause of this problem<sup>1-3</sup>. Iron deficiency during pregnancy is thought to be caused by multifactorial such as low-iron diet intake, malabsorption in gastrointestinal tract, parasitic diseases or short inter-pregnancy interval<sup>4</sup>. Iron deficiency anemia is associated with adverse pregnancy outcomes such as preterm delivery, low birth weight, and peri-partum blood transfusion<sup>5-7</sup>.

Iron requirement of pregnant women are greater than in the non-pregnant state. Approximately 1,000 mg of elemental iron is needed in normal pregnancy in addition to 500 mg of them is consumed for maternal red blood cell production<sup>8,9</sup>. Insufficient iron storage in pregnant women is generally observed, subsequently ordinary iron supplementation during pregnancy is beneficial<sup>10, 11</sup>. However, in previous studies' findings the compliant rate of iron supplement in pregnant women was merely 41.4-65.9%<sup>12-14</sup>. There are many factors association with non-regularly taking the iron tablet, such as gastrointestinal side effects, low educational status, late antenatal care (>16 weeks of gestation), and no receiving health education about the benefit of iron supplementation. Ugwu, et al. reported the leading obstacle to comply to daily iron intake was gastrointestinal side effects about 41.7%<sup>14</sup>. Several gastrointestinal side-effects of oral iron supplementation included heartburn, nausea, stomach cramping, constipation, diarrhea, and vomiting<sup>15</sup>.

World Health Organization (WHO) recommended daily iron and folic acid supplementation with 30-60 mg of elemental iron and 0.4 mg folic acid for pregnant women to prevent maternal anemia, puerperal sepsis, low birth weight, and preterm birth. If daily iron is not acceptable due to side-effects, and in populations with an anemic prevalence among pregnant women of less than 20%, then the intermittent oral iron and folic acid supplementation with 120 mg of elemental iron and 2.8 mg folic acid once weekly is recommended<sup>16</sup>. Prevalence of anemia among pregnant women aged 15-49 years in 2011 of the global survey, Thailand was categorized in the prevalence group of greater than 20%<sup>1</sup>. Therefore, daily iron supplementation is a routine practice for antenatal care in our setting. Though during antenatal care, we do a routine blood test to assess general health status including anemia, thalassemia, hepatitis, syphilis, and HIV infection. The women without anemia and some with high hemo-

globin concentration from blood test at initial visit, second trimester, and at term, they still received iron supplementation. So, we plan to evaluate the compliant rate and the hemoglobin concentration in second trimester through at term pregnancy among groups of different rates of compliance.

## Methods

This study was a questionnaire-based prospective cross-sectional study conducted at Srinagarind Hospital, a tertiary hospital in Khon Kaen, Thailand. Study protocol was approved by the Khon Kaen University Ethics Committee in Human Research (HE611623). All participants provided written informed consent before data collection. Regarding a compliance rate of 65.9% from a previous study<sup>16</sup>, with 95% confidence level and an error margin of 5%, the estimated sample size was at least 349.

Inclusion criteria counted in 18-year-old or older, term pregnancy, non-anemic status at initial blood test on antenatal care and received daily iron supplementations before 20 weeks of gestation. Non-anemic status was defined as hemoglobin level 11.0, 10.5, 11.0 gm/dl or more in first, second, and third trimester, respectively. Hemoglobin concentrations above 13 gm/dl was defined as high concentrated hemoglobin. Women with thalassemia disease or any contraindication for iron supplementation were excluded. The data gathered from participants after admission to the hospital for delivery. They were interviewed to obtain the personal data, regularity of daily taking the supplemented tablet and happening of side-effects (e.g. nausea, vomiting, abdominal cramping, bloating, constipation, and diarrhea). The compliance rate categorized as >80%, >50-80%, 25-50%, and < 25% according to the women's response that they took daily tablet of 6-7, 3-5, 2, and 0-1 days/week, respectively. Their medical records were reviewed to retrieve the type of supplementation and laboratory results of hemoglobin level during second trimester, and at term pregnancy. The protocol was conducted in the respect for the individual, the right to self-determination and the right to make informed decision regarding participation in the project, both initial and during the research which in accordance with the principles of the Declaration of Helsinki.

Descriptive statistics were used to describe the demographic baseline characteristics. Numerical data were expressed as mean, standard deviation, percentage and 95% confidence interval (CI) to demonstrate

the precision of the data. Categorical variables were expressed as percentage. A p-value < 0.05 was considered statistically significant.

**Results**

A total of 350 pregnant women were recruited between August 9, 2019 and June 15, 2020. From 350 questionnaires were implemented, 324 (92.57%) were complete filled out. Most of the incomplete data resulted of lacking to record hemoglobin level at term pregnancy. The participants' characteristics were shown in Table 1 as their mean aged of 29.30 years, majority of them in the aged range of 20-35 years. Almost 60% were the second pregnancy, while almost all (98%) had stable marital status. More than half had graduate education and none smoking exposure. Most of women received Triferdine (59.40%) while the second order was ObiminAZ (38.00%) as the tablet for iron supplementation. Triferdine is produced and supplied by the Government Pharmaceutical Organization, contained of iron 60.81 mg, potassium iodide 0.15 mg; folic acid 0.4 mg. ObiminAZ is the product of the commercial pharmaceutical company, contained ferrous fumarate 200 mg, iodine 0.2 mg, folic acid 1 mg, and vitamin A, B1, B2, B6, B12, C, D, E, nicotinamide, zinc, and calcium lactate. The compliance as in Table 2 demonstrated that almost 90% of participants had compliance rate of greater than 80%. There was none in the compliance rate of 25-50% and a few of women in compliance rate <25%.

In Table 3 showed the frequency and rate of side-effects occurrence among different compliance groups of iron supplementation. Mostly of reported side-effects were nausea and constipation. The less compliance rate found in the more proportion of side-effects occurrence as the results revealed that the total proportion of reported side-effects occurrence were 10.5%, 12.1%, 66.7% in >80%, >50-80%, <25% compliance groups, respectively.

In this study, the hemoglobin level in second trimester of pregnancy was evaluated vary between 28 and 36 weeks of gestation. According to the hospital protocol to take blood test for complete blood count, VDRL and anti-HIV in gestation of 28-32 weeks, however some of them were tested out of the hospital protocol range. Hemoglobin level at term was available in 324 from 350 women. The results in Table 4 and 5, there was no difference rate of anemia during second trimester between all groups of compliance

**Table 1** General characteristics of studied women

Characteristics	Number (%)
<b>Age (yrs.)</b>	
< 20	5 (1.43)
20 - 35	302 (86.29)
>35	43 (12.29)
<b>Parity</b>	
1	142 (40.57)
≥ 2	208 (59.43)
<b>Marital status</b>	
Married	343 (98.00)
Separated	6 (1.71)
Divorce	1 (0.29)
<b>Education levela</b>	
Under graduate	145 (41.43)
Graduate or above	205 (58.57)
<b>Smoking</b>	
Current smoking	5 (1.43)
Family members	142 (40.57)
none	203 (58.00)
<b>Type of iron supplementation (some of them had more than one type of supplementation)</b>	
Triferdine	208 (59.40)
ObiminAZ	133 (38.00)
Ferrous fumarate	14 (4.00)
Folic acid	18 (5.14)
others	13 (3.71)

a: Graduate and above = bachelor's degree or above

**Table 2** Compliance rate of iron supplementation

Compliance rate	number(%)	95%CI
>80 %	314 (89.71)	86.52-92.91
>50 - 80%	33 (9.43)	6.35-12.51
25 - 50 %	0 (0.00)	-
<25 %	3 (0.86)	0.00-1.83

**Table 3** Side-effects occurrence rate in different group of iron supplementation compliance

Side effects	>80% (N=33/314)		50-80% (N=4/33)		<25% (N=2/3)	
	No. (%)	95% CI	No. (%)	95% CI	No. (%)	95% CI
Nausea	14 (4.46)	2.46-7.37	3 (9.09)	1.91-24.33	2 (66.67)	9.43-99.16
vomiting	5 (1.60)	0.52-3.68	1 (3.03)	0.07-15.76	2 (66.67)	9.43-99.16
GI symptomsa	2 (0.64)	0.08-2.28	0 (0.00)	0.00-10.58	1 (33.33)	0.84-90.57
Constipation	18 (5.73)	3.43-8.91	1 (3.03)	0.08-15.76	0 (0.00)	0.00-70.76
Diarrhea	5 (1.59)	0.52-3.68	0 (0.00)	0.00-10.58	0 (0.00)	0.00-70.76
>1 of above symptoms	6 (1.91)	0.70-4.11	1 (3.03)	0.08-15.57	2 (66.67)	9.43-99.16

None of the participants were categorized into compliance 25-50% group.

a: GI symptoms = abdominal cramping/bloating

**Table 4** Effects of iron supplementation compliance rate on hemoglobin levels/anemia/high concentrated hemoglobin in the second trimester.

Compliance	Number (N=350)	Hemoglobin Mean ± SD	Anemic women <sup>a</sup> No.(%)	High concentrated hemoglobin women <sup>b</sup> No.(%)
>80%	314	12.00±0.88	7 (2.23)	38 (12.10)
>50-80%	33	11.92±1.06	2 (6.06)	4 (12.12)
25-50%	0	0	0 (0.00)	0 (0.00)
<25 %	3	12.00±0.92	0 (0.00)	0 (0.00)

<sup>a</sup>: Anemic women: Hb < 10.5 g/dl

<sup>b</sup>: High concentrated hemoglobin: Hb > 13 g/dl

**Table 5** Effects of iron supplementation compliance on hemoglobin levels/anemia/high concentrated hemoglobin at term pregnancy

Compliance	Number (N=350)	Hb Mean ± SD	Anemic women <sup>a</sup> No.(%)	High concentrated hemoglobin women <sup>b</sup> No.(%)
> 80%	291	12.67 ± 0.90	5 (1.72)	94 (32.30)
> 50 - 80%	31	12.49 ± 0.92	1 (3.23)	8 (25.81)
25 - 50%	0	0	0 (0.00)	0 (0.00)
< 25 %	2	11.00 ± 0.28	1 (50.00)	0 (0.00)

NB: Hb level available in 324 from 350 women

<sup>a</sup>: Anemic women: Hb < 11 g/dl

<sup>b</sup>: High concentrated hemoglobin: Hb > 13 g/dl

(p > 0.05). While at term pregnancy, rate of anemia was 50% (N=1/2, 95%CI: 1.25-98.74) in <25% compliance group. The lowest hemoglobin concentration was 9.7 g/dl in second trimester and was 9.9 g/dl at term of gestation, all of them were in >80% and >50-80% compliance groups. None of them had severe anemia.

In contrast, hemoglobin concentrations above 13 g/dl, which defined as high concentrated hemoglobin, were more frequently found in >80% compliance

group (12.10%, 95%CI: 8.71-16.23) and >50-80% compliance group (12.12%, 95%CI: 3.40-28.20) during second trimester. As well as at term pregnancy, 32.30% (95%CI: 26.96-38.00) in >80% compliance group and 25.81% (95%CI: 11.86-44.61) in >50-80% compliance group. There was no participant developed high hemoglobin concentration in <25% compliance group in second trimester and at term pregnancy period. The maximum hemoglobin concentrations were 15.4 gm/dl and 16.2 gm/dl during second trimester and at

term, respectively, all of them were in >80% compliance group.

### Discussion

Iron supplementation during pregnancy had been practiced for decades in developing country. According to WHO recommendation to implement daily iron supplementation during pregnancy to prevent pregnancy complications when the prevalence of anemia greater than 20%<sup>16</sup>. The last WHO global survey in 2011 publicized the prevalence of anemia in Thailand greater than 20%<sup>1</sup>. In view of that, routine iron supplementation in non-anemic pregnant women is also be practiced for antenatal care in this study setting. However, the study revealed that almost 90% of pregnant women had such a high compliance rate of >80%, the side effect rate was around 10%, they still had anemia in second trimester and at term 1-2%. Other than that they challenged with high hemoglobin concentration rate of 12% and 32% in second trimester and at term, respectively.

The iron supplementation is a recommended practice for antenatal care to improve pregnancy outcomes. Sometimes it can cause undesired side effects which is unable to tolerate in some women. In this study findings revealed such a high compliance rate of 89.7% when compared to other studies with high compliance rates of 80- 85%<sup>17</sup>. While there were low compliance rates in many studies of 20-60%<sup>17-19</sup>. Other than the side effects of iron supplementation might affect the compliance, in previous studies found that it may associate with marital status, maternal age, and educational level<sup>12,13, 19,20</sup>. In addition, the study's results showed that the more side-effects occurrence found in the less compliance rate as the results revealed that the total proportion of side-effects occurrence were 10.5%, 12.1%, 66.7% in >80%, 50-80%, <25% compliance groups, respectively. The result was consistent with those reported from previous studies that iron supplementation significantly increased risk of gastrointestinal side-effects, 19.7-63.3% of non-compliance women<sup>12, 15, 18,19</sup>.

In our study, though there was no significant difference of anemia developed during second trimester and at term pregnancy between all compliance groups. However, there was anemia in second trimester and at term 1-2% in >80% compliance group and found one of two woman developed anemia in <25% compliance group at term pregnancy. This was

contrast to previous studies that anemia was significantly associated with non-compliance of iron supplementation<sup>13,21,22</sup>. This inconsistent data may due to including nearly 30% of anemic women at initial of their studies. Other than that, our setting is a prevalence area of thalassemia that iron supplementation could not prevent anemia. So that we still found anemia in high compliance group.

Regarding to the study's findings that high hemoglobin concentration occurred with a substantial portion (12 - 32%) in high compliance groups. Although, there was lack of evidence indicating that iron supplementation can result in abnormally high hemoglobin concentration<sup>20</sup>. However, without iron supplementation during pregnancy would not be anemia in women with hemoglobin level greater than 13.2 g/dl<sup>21</sup>. Hemoglobin level greater than 13.0 gm/dl was associated with small for gestational age, still-birth, preeclampsia, gestational diabetes, low birth weight and preterm delivery<sup>23,24</sup>. Thus, health-care providers should take more precaution to offer iron supplementation for non-anemic pregnant women to avoid maternal high hemoglobin concentration status and diminish undesirable side-effects. Otherwise, intermittent iron supplementation, daily tablet for 2-3 days/week, should be encouraged to apply in non-anemic pregnant women<sup>11,16</sup>.

The strengthening results of this study may account to that all information to evaluate the compliance of taking daily iron supplementation was obtained directly from participants who provided well co-operative response on concerning of the effect on their pregnancy outcomes if they could not take enough tablet. Nonetheless, it had too small number of participants in less compliance groups to assess the factors that may affect the compliance other than the side effects. In addition, further study to assess if it is necessary to implement iron supplementation in non-anemic women in the setting with routine blood testing for anemia during antenatal care at the initial visit and in second trimester.

### Conclusions

We found high compliance rate of iron supplementation in non-anemic pregnant women, with the more occurrence of side-effects had the less compliance. While anemia still appeared in high compliance women, where anemia due to other cause, e.g., thalassemia, should be concerned. Other than that high hemoglobin concentration

substantially be found in high compliance group. Therefore, health-care providers should keep more thoughtfulness in the women who have hemoglobin level greater than 13 g/dl on initial visit of antenatal care before implementing routine iron supplementation to avoid maternal high hemoglobin concentration status and diminish undesirable side-effects.

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