Compliance of daily iron supplementation during pregnancy affecting the hemoglobin level in second trimester and at term

Romthira - Srisai

Khon Kaen University

Jadsada Thinkhamrop (✉ jadsada@kku.ac.th)

Khon Kaen University <https://orcid.org/0000-0002-0260-2131>

Sukanya - Chaiyarach

Khon Kaen University Faculty of Medicine

Sukanya - Kreetiyutanont

Khon Kaen University Faculty of Medicine

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Abstract

Objectives: To determine the compliance rate of iron supplementation during pregnancy and the hemoglobin concentration in second trimester and at term.

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 days/week, respectively. The type of supplementation and laboratory results of hemoglobin level were retrieved from their medical records.

Results: Almost 90% of 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. In second trimester and term pregnancy revealed some anemic women. 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: There was high compliance rate of iron supplementation with the high hemoglobin level markedly found in high compliance group.

Background

Worldwide prevalence of anemia among pregnant women was 41.8% and iron deficiency anemia is the most common cause of this problem (1–3). 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 (4). Iron deficiency anemia was associated with adverse pregnancy outcomes such as preterm delivery, low birth weight, and peri-partum blood transfusion (5–7).

Iron requirement of pregnant women are greater than in the non-pregnant state. Approximately 1000 mg of elemental iron is needed in normal pregnancy in addition to 500 mg of them is consumed for maternal red blood cell production (8–9). Insufficient iron storage in pregnant women are generally observed, subsequently ordinary iron supplementation during pregnancy is beneficial (10–11). However, in previous studies' findings the compliance rate of iron supplement in pregnant women were merely 41.4–65.9% (13–15). 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. (2014) reported the leading obstacle to comply to daily iron intake was gastrointestinal side effects about 41.7%. Several gastrointestinal side-effects of oral iron supplementation included heartburn, nausea, stomach cramping, constipation, diarrhea, and vomiting (16).

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 (12). 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% (1). 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 hemoglobin concentration from blood test at initial visit, second trimester, and at term, they still received iron supplementation. So, we plan to evaluate the compliance rate and the hemoglobin concentration in second trimester through at term pregnancy among groups of different rate 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 (15), 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 initially and during the course of 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, percentages and 95% confidence interval (CI) to demonstrate the precision of the data. Categorical variables were expressed as percentages. 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 (92.6%) were completely 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 29.3 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 them received Triferdine (59.4%) and ObiminAZ (38.0%) 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%.

Table 1
General characteristics of studied women

Characteristics		number	percentage
Age (yrs.)	< 20	5	1.43
	20–35	302	86.29
	> 35	43	12.29
Parity	1	142	40.57
	≥ 2	208	59.43
Marital status	Married	343	98.00
	Separated	6	1.71
	Divorce	1	0.29
Education level ^a	Under graduate	145	41.43
	Graduate or above	205	58.57
Smoking	Current smoking	5	1.43
	Family members	142	40.57
	none	203	58.00
Type of iron supplementation (some of them had more than one type of supplementation)	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	Percentage (%)	95%CI
> 80%	314	89.71	86.52–92.91
> 50–80%	33	9.43	6.35–12.51
25–50%	0	-	-
< 25%	3	0.86	0.00-1.83

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 side-effects occurrence were 10.5%, 12.1%, 66.7% in > 80%, > 50–80%, < 25% compliance groups, respectively.

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 symptoms ^a	2	0.64	0.08–2.28	0	0	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	0.00–70.76
Diarrhea	5	1.59	0.52–3.68	0	0	0.00–10.58	0	0	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									

In this study, the hemoglobin level in second trimester of pregnancy were 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 Tables 4 and 5, there was no difference rate of anemia during second trimester between all groups of compliance (p-value > 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 gm/dl in second trimester and was 9.9 gm/dl at term of gestation, all of them were in > 80% and > 50–80% compliance groups. None of them had severe anemia.

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

Compliance	Number (N = 350)	Hb Mean ± SD	Anemic women ^a		High concentrated hemoglobin women ^b	
			Number	%	Number	%
> 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	0	0
< 25%	3	12.00 ± 0.92	0	0	0	0
a: Anemic women: Hb < 10.5 gm/dl						
b: High concentrated hemoglobin: Hb > 13 gm/dl						

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

Compliance	Number (N = 324)	Hb Mean $\pm$ SD	Anemic women ^a		High concentrated hemoglobin women ^b	
			Number	%	Number	%
> 80%	291	12.67 $\pm$ 0.90	5	1.72	94	32.30
> 50–80%	31	12.49 $\pm$ 0.92	1	3.23	8	25.81
25–50%	0	0	0	0	0	0
< 25%	2	11.00 $\pm$ 0.28	1	50.00	0	0
NB: Hb level available in 324 from 350 women						
a: Anemic women: Hb < 11 gm/dl						
b: High concentrated hemoglobin: Hb > 13 gm/dl						

In contrast, hemoglobin concentrations above 13 gm/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%(12). The last WHO global survey in 2011publicized the prevalence of anemia in Thailand greater than 20% (1). 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 effects 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 found such a high compliance rate of 89.7% when compared to other studies with high compliance rates of 80–85% (18). While there were low compliance rates in many studies of 20–60% (17–19). 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 (13–14, 19, 21). 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 (13, 16–17, 19).

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 significant associated with non-compliance of iron supplementation (14, 22–23). This inconsistent data may due to including nearly 30% of anemic women at initial of their studies. Other than that, in 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 (21). However, without iron supplementation during pregnancy would not be anemia in women with hemoglobin level greater than 13.2 gm/dl (22). Hemoglobin level greater than 13.0 gm/dl was associated with SGA, stillbirth, preeclampsia, gestational diabetes, low birth weight and preterm delivery (24–25). 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 should be encouraged to apply in non-anemic pregnant women (11–12).

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 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 gm/dl on initial visit of antenatal care before implementing routine iron supplementation to avoid maternal high hemoglobin concentration status and diminish undesirable side-effects.

Abbreviations

Hb: hemoglobin

gm/dl: gram/deciliter

mg: milligram

WHO: World Health Organization

HIV: Human Immunodeficiency Virus

VDRL: Venereal Diseases Research Laboratory

CI: confidence interval

SD: standard deviation

SGA: small for gestational age

Declarations

Acknowledgment

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Ethics approval and consent to participate

Study protocol was approved by the Khon Kaen University Ethics Committee in Human Research (HE611623) before starting data collection. All participants provided written informed consent before data collection.

Consent to publish

Not applicable

Availability of data

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interest

The authors report no conflicts of interest in this work which related to any relationships that may be deemed to influence the objectivity of the study. None of authors had any commercial associations, either directly or through immediate family, in areas such as expert testimony, consulting, honoraria, stock holdings, equity interest, ownership, patent-licensing situations or employment that might pose a conflict of interest and had no personal relationships or academic competition.

Authors' contributions

RS and JT contributed on the conception, design, analysis and interpretation of the project work, including drafting and revising critically on the final version of the manuscript. SC and SK involved in data collection and management, approved the final version on accountable for all aspects of the study.

References

1. WHO | The global prevalence of anaemia in 2011 [Internet]. WHO. [cited 2020 Aug 16]. Available from: http://www.who.int/entity/nutrition/publications/micronutrients/global_prevalence_anaemia_2011/en/index.html
2. Lee AI, Okam MM. Anemia in pregnancy. Hematol Oncol Clin North Am. 2011 Apr;25(2):241–259, vii.

3. Auerbach M, Abernathy J, Juul S, Short V, Derman R. Prevalence of iron deficiency in first trimester, nonanemic pregnant women. *J Matern-Fetal Neonatal Med Off J Eur Assoc Perinat Med Fed Asia Ocean Perinat Soc Int Soc Perinat Obstet.* 2019 Jun 3;1–4.
4. Casey GJ, Montresor A, Cavalli-Sforza LT, Thu H, Phu LB, Tinh TT, et al. Elimination of Iron Deficiency Anemia and Soil Transmitted Helminth Infection: Evidence from a Fifty-four Month Iron-Folic Acid and De-worming Program. *PLoS Negl Trop Dis.* 2013;7(4):e2146.
5. VanderMeulen H, Strauss R, Lin Y, McLeod A, Barrett J, Sholzberg M, et al. The contribution of iron deficiency to the risk of peripartum transfusion: a retrospective case control study. *BMC Pregnancy Childbirth.* 2020 Apr 6;20(1):196.
6. Athe R, Dwivedi R, Pati S, Mazumder A, Banset U. Meta-analysis approach on iron fortification and its effect on pregnancy and its outcome through randomized, controlled trials. *J Fam Med Prim Care.* 2020 Feb;9(2):513–9.
7. Col Madendag I, EraslanSahin M, Madendag Y, Sahin E, Demir MB, Acmaz B, et al. The Effect of Iron Deficiency Anemia Early in the Third Trimester on Small for Gestational Age and Birth Weight: A Retrospective Cohort Study on Iron Deficiency Anemia and Fetal Weight. *BioMed Res Int.* 2019;2019:7613868.
8. Stevens GA, Finucane MM, De-Regil LM, Paciorek CJ, Flaxman SR, Branca F, et al. Global, regional, and national trends in haemoglobin concentration and prevalence of total and severe anaemia in children and pregnant and non-pregnant women for 1995-2011: a systematic analysis of population-representative data. *Lancet Glob Health.* 2013 Jul;1(1):e16-25.
9. Kavle JA, Stoltzfus RJ, Witter F, Tielsch JM, Khalfan SS, Caulfield LE. Association between Anaemia during Pregnancy and Blood Loss at and after Delivery among Women with Vaginal Births in Pemba Island, Zanzibar, Tanzania. *J Health Popul Nutr.* 2008 Jun;26(2):232–40.
10. Agbozo F, Abubakari A, Der J, Jahn A. Maternal Dietary Intakes, Red Blood Cell Indices and Risk for Anemia in the First, Second and Third Trimesters of Pregnancy and at Predelivery. *Nutrients.* 2020 Mar 15;12(3).
11. Peña-Rosas JP, De-Regil LM, Garcia-Casal MN, Dowswell T. Daily oral iron supplementation during pregnancy. *Cochrane Database Syst Rev.* 2015 Jul 22;(7):CD004736.
12. WHO | WHO recommendations on antenatal care for a positive pregnancy experience [Internet]. WHO. [cited 2020 Aug 9]. Available from: http://www.who.int/reproductivehealth/publications/maternal_perinatal_health/anc-positive-pregnancy-experience/en/
13. Ugwu EO, Olibe AO, Obi SN, Ugwu AO. Determinants of compliance to iron supplementation among pregnant women in Enugu, Southeastern Nigeria. *Niger J Clin Pract.* 2014 Sep 1;17(5):608.
14. Habib F, Alabdin EHZ, Alenazy M, Nooh R. Compliance to iron supplementation during pregnancy. *J ObstetGynaecol J Inst ObstetGynaecol.* 2009 Aug;29(6):487–92.
15. Sendeku FW, Azeze GG, Fenta SL. Adherence to iron-folic acid supplementation among pregnant women in Ethiopia: a systematic review and meta-analysis. *BMC Pregnancy Childbirth.* 2020 Mar 4;20(1):138.
16. Tolkien Z, Stecher L, Mander AP, Pereira DIA, Powell JJ. Ferrous sulfate supplementation causes significant gastrointestinal side-effects in adults: a systematic review and meta-analysis. *PloS One.* 2015;10(2):e0117383.
17. Taye B, Abeje G, Mekonen A. Factors associated with compliance of prenatal iron folate supplementation among women in Mecha district, Western Amhara: a cross-sectional study. *Pan Afr Med J.* 2015;20:43.
18. Birhanu TM, Birarra MK, Mekonnen FA. Compliance to iron and folic acid supplementation in pregnancy, Northwest Ethiopia. *BMC Res Notes.* 2018 May 30;11(1):345.
19. Gebremedhin S, Samuel A, Mamo G, Moges T, Assefa T. Coverage, compliance and factors associated with utilization of iron supplementation during pregnancy in eight rural districts of Ethiopia: a cross-sectional study.

BMC Public Health. 2014 Jun 14;14:607.

20. Sloan NL, Jordan E, Winikoff B. Effects of iron supplementation on maternal hematologic status in pregnancy. *Am J Public Health*. 2002 Feb;92(2):288–93.
21. Yip R. Significance of an abnormally low or high hemoglobin concentration during pregnancy: special consideration of iron nutrition. *Am J Clin Nutr*. 2000;72(1 Suppl):272S–279S.
22. Alizadeh L, Salehi L. Is Routine Iron Supplementation Necessary in Pregnant Women With High Hemoglobin? *Iran Red Crescent Med J*. 2016 Jan;18(1):e22761.
23. Young MF, Oaks BM, Tandon S, Martorell R, Dewey KG, Wendt AS. Maternal hemoglobin concentrations across pregnancy and maternal and child health: a systematic review and meta-analysis. *Ann N Y Acad Sci*. 2019 Aug;1450(1):47–68.
24. Steer PJ. Maternal hemoglobin concentration and birth weight. *Am J Clin Nutr*. 2000 May 1;71(5):1285S–1287S.
25. Murphy JF, O’Riordan J, Newcombe RG, Coles EC, Pearson JF. Relation of haemoglobin levels in first and second trimesters to outcome of pregnancy. *Lancet Lond Engl*. 1986 May 3;1(8488):992–5.

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