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Adherence Does Not Guarantee the Outcome of Iron Supplementation for Reproductive-Age Women With Anemia in West Papua Province, Indonesia: A Quasi-experimental Study

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Abstract

Objectives: Monitoring iron supplementation effectiveness in the affected populations is important in assuring its success. The research objective of this study is to evaluate the effectiveness of iron supplementation and its related factors in increasing the hemoglobin levels of women with anemia that reside in the area of Teluk Bintuni Regency in West Papua Province, Indonesia.

Materials and Methods: A quasi-experimental study was performed to determine the changes in hemoglobin levels and the adherence between two supplementation groups (before and after supplementation). From the initial screening of hemoglobin levels of 875 reproductive-age women, 110 women with moderate and severe anemia were enrolled for a month-long iron supplementation therapy. This study was conducted from September 2018 until November 2019 at Teluk Bintuni Regency, West Papua, Indonesia. The changes in hemoglobin levels were measured after 30 days of iron supplementation. The associated factors, including participants' characteristics, chronic energy deficiency (CED) levels, adherence to supplementation programs, and knowledge of anemia, were also assessed. The adherence level to the supplementation was measured using the Medication Adherence Rating Scale (MARS) questionnaires and the pill counting method.

Results: The mean hemoglobin level significantly increased from 9.12±1.70 before supplementation to 10.15±1.65 after 30 days ($P<0.001$). Interestingly, results from the MARS questionnaires and pill counting method suggested that only 76% and 66% of participants adhered to the supplementation program, respectively. Further univariate analysis showed that adherence, ethnicity, and type of supplementation were factors that may influence the success of the iron supplementation therapy.

Conclusions: Based on this study findings, it can be concluded that anemia is related to various factors, and its implementation should be carefully monitored, not solely depending on individual adherence.

Keywords: Iron, Dietary supplement, Anemia, Women, Treatment adherence

Introduction

Anemia is one of the global sustained development goals, with a targeted 50% decrease in anemia prevalence in women of reproductive age (WRA) in 2025 (1). In 2016, the standard prevalence of anemia among pregnant women from 38 Asian nations was 34.7% (2). Anemia can be affected by many factors. As stated by the World Health Organization (WHO), anemia can be diagnosed when the hemoglobin concentration of non-pregnant women is <12.0 g/dL and <11.0 g/dL in pregnant women (3).

In 2018, the prevalence of pregnant women with anemia increased to 48.9% in Indonesia, with the highest average found in young adults, whose ages ranged from 15-24 years (4). The Indonesian government has implemented an iron supplementation program specifically intended for WRA. According to a report from the Indonesian Ministry of Health, 81% of WRA in the West Papua Province who had iron supplementation were pregnant women (5). Furthermore, the rate of childbirth in adolescent girls aged 15-19 years was relatively high in the West Papua Province, whereas in Kaimana, Sorong, and Manokwari Regency was 66, 53, and 44 per 1000 women, respectively (6). Therefore, iron supplementation will continue for all menstruating teenage girls. In Teluk Bintuni Regency of the West Papua province, the supplementation program assessment has been limited to the distribution of supplements, with the addition of the percentage of target achievement was based on the verbal answers of respondents on whether or not to consume iron supplements (5), which may cause many biases in the evaluation.

Thus, in this study, we evaluated the effectiveness of iron supplementation in increasing hemoglobin levels. We also analyzed the factors that directly influence the success of the iron supplementation program.

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Key Messages

- Reproductive-age women in West Papua, Indonesia, have poor knowledge about anemia.
- Ethnicity plays a role in the success of iron supplementation therapy.
- Iron supplementation should be closely monitored to maintain individual adherence.

Materials and Methods

Study Design and Participants

This quasi-experimental (before and after study) was performed at the primary healthcare centers of six districts in Teluk Bintuni Regency, West Papua province, Indonesia, from September 2018 to November 2019. A total of 110 participants aged between 15-49 years old with moderate and severe anemia, according to their initial hemoglobin levels, were enrolled to this study. Our sampling method was total population sampling; all participants who met the inclusion and exclusion criteria will be included in the study. Hemoglobin levels were measured before and after the iron supplementation intervention.

The anemia categories are considered as follows: in non-pregnant women, hemoglobin levels between 11.9 and 11.0 g/dL were classified as mild anemia, 10.9-8.0 g/dL as moderate anemia, and 8.0 g/dL as severe anemia. Meanwhile, hemoglobin levels of 10.9-10.0 g/dL were classified as mild anemia in pregnant women, 9.9-7.0 g/dL as moderate anemia, and 7.0 g/dL as severe anemia (3).

Inclusion and Exclusion Criteria

The inclusion criteria were women aged 15–49 with moderate or severe anemia. All participants with incomplete data, pregnant women, and those receiving other supplementation were excluded from the study. To avoid iron overload, participants with mild anemia were ruled out of this study.

Sample Size

We performed total population sampling. In the initial screening, 875 reproductive-age women were included for hemoglobin level testing. As a result, 110 participants with moderate to severe anemia were enrolled in this study for a month of iron supplementation therapy.

Interventions

We randomly divided the participants into two groups for interventions. Each group consumed a different type of oral iron salt supplement that was given on day 0. Each participant was given 30 tablets, one to be taken daily for 30 days. This iron supplementation was administered based on WHO guidelines. The first group received Iron Fumarate-Folic Acid supplement that contains the elemental iron equivalent of 30 mg and 400 µg of folic acid. On the other hand, the second group received Iron Gluconate-Multivitamins supplement contains the basic iron equivalent of 0.9 mg, 500 µg of folic acid, and multivitamins, such as 15 mg vitamin B1 HCl, 0.25 mg vitamin B2, 0.25 mg vitamin B6 HCl, 12.5 mg vitamin C, 1.5 mg calcium pantothenate, 10 mg nicotinamide, 0.5 mg folic acid, 0.65 mg cupric sulfate, and 100 mg of dried beef liver (7,8). There are 69 and 41 participants in the first and second groups, respectively.

Data Collection

Surveys on demographic characteristics, including age, ethnicity, education level, living conditions, the habit of chewing betel nuts, and health status, were also conducted on all participants before the iron supplementation intervention. Bodyweight was measured during the interview, and chronic energy deficiency (CED) was calculated based on the Food and Agriculture Organization protocols using the respondents' mid-upper arm circumference. When the mid-upper arm circumference was <23.5 cm, the participant was categorized as having a CED condition (9).

Iron Supplementation Intervention and Hemoglobin Measurement

This study used two types of iron supplementation as the intervention, which are Fe fumarate-folic acid and Fe gluconate-multivitamins (Livron), both produced by PT Rajawali Nusantara Indonesia, Indonesia. The hemoglobin level was assessed onsite by utilizing the HemoCue analyzer (HemoCue 201™, Angelholm, Sweden), as the manufacturer instructed. An amount of 10 µL of blood was collected from the participant's finger and applied to the portable HemoCue hemoglobin analyzer. The results were obtained immediately using the cyanmethemoglobin principle, and the instrument was ready to be used for subsequent measurements. (3,10).

Outcome Measurement

In this study, two main outcomes were measured: the level of hemoglobin and participants' adherence. Factors associated with successful therapy for anemia were regarded as the secondary outcome. One day after the supplementation period, all participants were followed up with another hemoglobin measurement and a follow-up questionnaire regarding their adherence and knowledge of anemia. The adherence level was assessed using the Medication Adherence Rating Scale (MARS) (11), using a validated Indonesian translation, and shown to be valid and reliable after initially testing 30 local respondents in Teluk Bintuni Regency. The results show that the questionnaire was valid with a Pearson product-moment correlation and reliable with a moderate Cronbach's alpha value of 0.659 (moderate range value of $0.50 < \alpha < 0.70$) (12, 13). Furthermore, the adherence level was also measured using the pill counting method, which is commonly used to analyze the adherence level of participants with oral medication over a long period of time. If <20% of the total

30 tablets were found to be remaining (unconsumed), the participants were considered to adhere to the program (14). The knowledge of anemia was measured using the open questionnaires developed by Dinga (15).

Statistical Analysis

Participant characteristics and outcome measures were reported using descriptive statistics. Participants' characteristic data were presented in percentages, while the hemoglobin level and adherence score were presented in means. Fisher exact test, Pearson χ^2 test, and Wilcoxon test were utilized to assess the associations of univariate variables with the binary outcomes. A *P* value of less than 0.05 was determined as the level of statistical significance. Statistical Package for the Social Sciences (SPSS) version 25 was used to conduct all statistical analyses (IBM Corp., Armonk, NY, USA).

Results

Sociodemographic Characteristics and Hemoglobin Levels

We used the minimum standard cutoff of 2.00 g/dL to include the successful category of iron supplementation intervention in a 1-month durational study. A total of 467 of the 875 initial participants (53.3%) were found to have anemia, whereas 110 of them (12.6%) were identified as having moderate or severe anemia and were recruited for the month-long iron supplementation study. A complete flowchart representing participant recruitment can be seen in Figure 1. Of the 110 participants enrolled in the iron supplementation program, 62% were young women aged 15-20 years; 66% were of Papuan ethnicity; 48% were junior high school graduates; 64% lived in rural areas; and 58% had the habit of chewing betel nuts. The mean bodyweight of the participants was 50.32 ± 9.66 kg, 74% of whom had no CED. The complete sociodemographic and anthropometric data can be seen in Table 1. After 30 days of iron supplementation, the mean hemoglobin level was found to have increased from 9.12 ± 1.70 g/dL to 10.15 ± 1.65 g/dL (Table 2).

Adherence to Iron Supplementation Program

The MARS questionnaires and pill counting used to measure adherence suggested relatively similar results. The MARS measurements indicated that 76% of the participants were taking the supplements with good adherence. In contrast, pill counting measurements suggested that 66% of the participants had less than six tablets remaining (Table 1). More than half of the participants showed high adherence to taking iron supplements every day according to the dosage and usage instructions for 30 days. However, there was a significant difference between hemoglobin levels and the participants' adherence to the MARS and pill counting methods before and after supplementation (Table 3). Only 21 participants (19.1%) had a successful outcome of more than or equal to a 2 g/dL increase in hemoglobin levels, while 80.9% of the remaining 89 participants had less than a 2 g/dL increase (Table 4).

Knowledge of Anemia

Participants gave correct answers to questions on the definition, causes, and effects or symptoms of anemia with percentages of 38%, 39%, and 39%, respectively (Table 1), which means that only a few have sufficient knowledge about anemia. Poor knowledge contributes to the inhibition of iron absorption caused by factors that cannot be controlled by supplementation alone; only 19.1% of 110 participants achieved the targeted hemoglobin levels.

Contributing Factors to The Outcome of Iron Supplementation

Twelve factors were analyzed for their relation to the success of iron supplementation therapy for anemia (Table 4). The type of supplements showed a significant association with the successful intervention ($P = 0.015$).

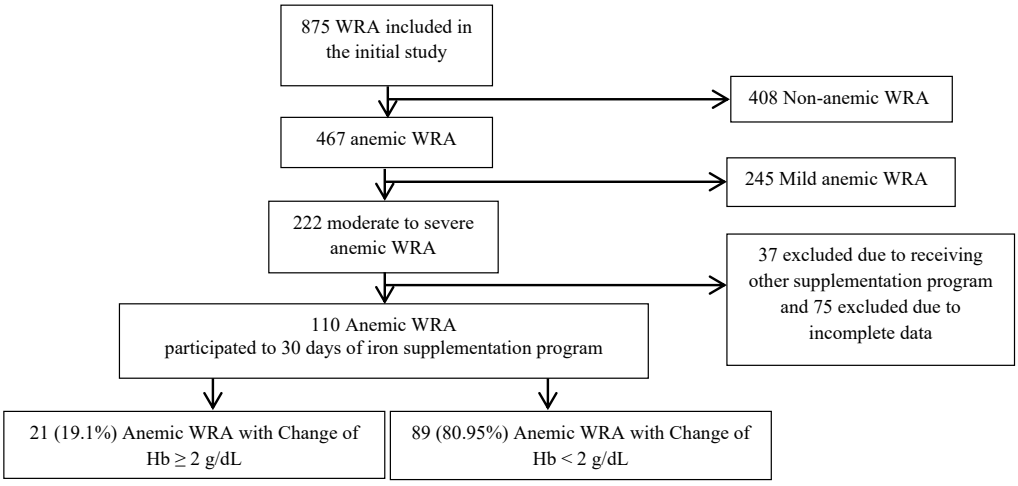

Figure 1. The Study CONSORT Flowchart. Abbreviation: WRA, woman reproductive age.

Table 1. Sociodemographic Characteristics of the Study Participants

Parameters	Number	Percent
Age group (y)		
15–20	68	62
21–25	10	9
26–30	10	9
31–35	9	8
36–40	7	6
41–45	5	5
46–49	1	1
Ethnicity		
Non-Papuan	37	34
Papuan	73	66
Education level		
No education	6	5
Elementary school	26	24
Junior high school	53	48
Senior high school	20	18
University	5	5
Residence		
Rural	70	64
Urban	40	36
Betel nut habit		
Yes	64	58
No	46	42
Chronic energy deficiency		
Yes	29	26
No	81	74
Adherence by pill counting		
Low adherence	37	34
High adherence	73	66
Adherence by MARS		
Low adherence	26	24
High adherence	84	76
Type of Iron Supplements		
Iron fumarate-folic acid	69	63
Iron gluconate-multivitamins	41	37
Knowledge of anemia definition		
Poor	68	62
Good	42	38
Knowledge of the causes of anemia		
Poor	67	61
Good	43	39
Knowledge of the effects of anemia		
Poor	67	61
Good	43	39

MARS: Medication Adherence Rating Scale.

Discussion

In Teluk Bintuni Regency, although the maternal mortality rate has decreased since 2018, anemia (moderate to severe) in WRA remains very high. In our study, of 110 subjects with moderate and severe anemia, 62% were teenagers aged 15-20 years, and 48% were still active in high school education. Adolescence is an important period because there is increased growth of muscle mass and the development of reproductive organ function, thus, requiring more blood volume. The red blood cells contain hemoglobin, which requires more heme iron. However, teenagers were unnoticed by parents as they continued to consume monotonous diets (16). This situation was further worsened by the betel nut chewing habit in the West Papua Province. In our study, 58% of the participants with moderate and severe anemia turned out to have this lifestyle. One of these betel nuts chewing ingredients is calcium powder made from a seashell. As calcium may inhibit iron absorption (17), this habit may worsen anemia (18).

Various factors can cause anemia. According to some studies, infection, pregnancy, malnutrition, inflammation, neoplasia, chronic blood loss, iron malabsorption, irregular eating habits, and low socioeconomic status could contribute to anemia. However, the cause of anemia in this study population is still poorly investigated by the authorities in the Teluk Bintuni Regency. Most individuals in developing countries develop anemia due to malnutrition, parasitic infection, chronic disease, or hemoglobinopathies. Meanwhile, anemia in developed countries may be attributed to gastrointestinal and genitourinary disorders and iron malabsorption (19, 20). The findings of this study indicate that school-aged girls are more likely than other age groups to have moderate or severe anemia. Moreover, young women are susceptible to anemia due to increased activities and blood loss during menstruation.

Furthermore, other factors associated with anemia are the consumption of safe drinking water, sanitation, and hygiene (21). Health and water facilities are commonly

Table 2. Hemoglobin Levels Before and After Iron Supplementation Program

Times	Hemoglobin (Hb) Level (g/dL)	Range	95% CI	*P* Value[a]
Before supplementation treatment	9.12±1.70	3.10-10.90	8.79-9.44	<0.001
After supplementation treatment	10.15 ± 1.65	5.20-14.10	9.83-10.46	

Data presented as mean ± standard deviation (SD); [a] Wilcoxon test.

Table 3. Comparison Between Adherence and Hemoglobin Levels Before and After Supplementation

Level of Adherence	Hemoglobin Level (g/dL)		*P* Value[a]
	Before	After	
MARS			
Low (n=26)	8.96 ± 1.41	9.89 ± 1.90	0.008
High (n=84)	9.16 ± 1.78	10.23 ±1.57	<0.001
Pill counting			
Low (n=37)	9.14 ± 1.44	10.02 ± 1.86	<0.001
High (n=73)	9.10 ± 1.83	10.21 ± 1.55	<0.001

MARS: Medication Adherence Rating Scale. Data presented as mean ± standard deviation (SD); [a] Wilcoxon test.

Table 4. Univariate Associations With the Successful Therapy of Anemia

Characteristic	Successful Treatment		*P* Value
	Yes (n=21)	No (n=89)	
Age (y)			
15–20	13 (61.9)	55(61.8)	
21–25	1 (4.8)	9 (10.1)	
26–30	2 (9.5)	8 (9.0)	
31–35	1 (4.8)	8 (9.0)	0.728[a]
36–40	3 (14.3)	4 (4.5)	
41–45	1 (4.8)	4 (4.5)	
46–49	0	1 (1.1)	
Ethnicity			
Non-Papuan	4 (19.0)	33(37.1)	0.116[b]
Papuan	17 (81.0)	56(62.9)	
Education level			
No Education	1 (4.8)	5 (5.6)	
Elementary School	3 (14.3)	23 (25.8)	
Junior high School	12 (57.1)	41(46.1)	0.860[a]
Senior High School	4 (19.0)	16 (18.0)	
University	1 (4.8)	4 (4.5)	
Residence			
Rural	15 (71.4)	55 (61.8)	0.409[b]
Urban	6 (28.6)	34 (38.2)	
Betel nut habit			
Yes	14 (66.7)	50 (56.2)	0.381[b]
No	7 (33.3)	39 (43.8)	
Chronic energy deficiency			
Yes	5 (23.8)	24 (27.0)	0.768[b]
No	16 (76.2)	65 (73.0)	
Adherence by pill counting			
Low Adherence	4 (19.0)	33 (37.1)	0.116[b]
High Adherence	17 (81.0)	56 (62.9)	
Adherence by MARS			
Low Adherence	7 (33.3)	19 (21.3)	0.245[b]
High Adherence	14 (66.7)	70 (78.7)	
Type of iron supplements			
IF-FA	18 (85.7)	51 (57.3)	**0.015[b]**
IG-MV	3 (14.3)	38 (42.7)	
Knowledge of Anemia Definition			
Poor	14 (66.7)	54 (60.7)	0.611[b]
Good	7 (33.3)	35 (39.3)	
Knowledge of the causes of anemia			
Poor	12 (57.1)	55 (61.8)	0.694[b]
Good	9 (42.9)	34 (38.2)	
Knowledge of the effects of anemia			
Poor	16 (76.2)	72 (80.9)	0.628[b]
Good	5 (23.8)	17 (19.1)	

MARS: Medication Adherence Rating Scale.
Data presented as No. (%).[a] Fisher-exact test; [b] Pearson χ^2 test.

well maintained in high-income countries' countryside and city areas (21,22). Interestingly, calcium hydroxide powder and betel nuts used to make the traditional Papuan chewing gum may contribute to iron deficiency. This traditional chewing gum is widely consumed in Papua by people of all ages, including children and the elderly. Calcium inhibits the absorption of iron particles dissolved in the blood vessels, which are required to form erythrocytes that supply nutrients to cells (23,24).

The surveys on the knowledge of anemia suggested that more than half of the participants have a poor understanding of what anemia is, what may cause anemia, and what may be affected by anemia (Table 1). In a previous study conducted in Tehran, a linear correlation between knowledge, attitude, and practice was discovered among women with anemia, implying that insufficient knowledge about anemia will affect the outcome of therapy (25). This lack of knowledge may affect WRAs who have never been pregnant. As countries focus on prenatal health to reduce maternal and child mortality (26), there has been a lack of education and awareness about anemia in non-pregnant women. Furthermore, pregnant women who have experienced pregnancy have better knowledge of anemia due to frequent visits to primary health care facilities to learn about health education, including knowledge about anemia (26, 27). Therefore, women who have never been pregnant have insufficient knowledge of anemia (28, 29).

Although the study participants have poor knowledge of anemia, their adherence to iron supplementation remains high. Our findings were consistent with a study conducted in Denmark (30), where pregnant women adhere to iron supplementation at a high rate. Meanwhile, a study in Brazil showed that pregnant women with lower education and low economic status have low adherence to iron supplementation, which amounts to only 35% of the prescribed iron supplementation (31). High compliance with iron supplementation therapy and good knowledge of anemia do not guarantee an increase in hemoglobin levels, as many biological conditions of participants with anemia are contraindicated with iron supplementation therapy (32-34). For example, when the body is in an infected state, it will worsen in the presence of iron; pathogens in the body will stimulate the plasma cell protector to increase resistance in the presence of iron (35-37). Another example of contraindication is when the participant's hepcidin levels are high, which decreases the absorption of iron in the intestine (38, 39). Therefore, despite the increase in compliance, the next dose of iron is ineffective because the body will not absorb it. Iron supplementation also causes a significant increase in gastrointestinal adverse effects, such as irritable bowel disease and constipation (40).

The high compliance to supplementation in the current study may also be due to the Hawthorne effect caused by participants' behavioral changes due to their awareness of being investigated (41). However, conventional therapeutic options, such as ferrous sulfate, a type of oral iron supplementation, are economical and simple despite the taste and adverse effects (gastrointestinal intolerance). Only a few studies have examined the outcome of iron supplementation therapy using biological changes, such as the increase in hemoglobin in red blood cells, as the cellular target of the treatment.

In the current study, a 1-month iron supplementation program with a minimum escalation in hemoglobin contents of 2.00 g/dL was considered successful (42).

When hemoglobin levels do not rise as expected and iron supplementation is continued, participants with anemia may be at an elevated risk of an oxidation reaction attributed to the prevalence of non-transferrin-bound iron that may act as free radicals in the body (43-45). Furthermore, there is also an enhanced risk of infection due to the pathogenicity of microorganisms in the presence of free iron (46). Therefore, in an iron supplementation program, the hemoglobin levels of participants should be monitored to evaluate whether the supplementation should be continued or stopped to begin the search for any underlying causes of anemia, such as pregnancy, infections, cancer, and hemoglobinopathy (47-49).

Additionally, several factors besides adherence indicate a health intervention's success, particularly in the case of iron supplementation. Our study discovered that a month of iron supplementation could achieve the treatment goal in women with moderate and severe anemia. The WHO recommends at least three months of daily iron supplementation in areas with a high burden on public health (prevalence of anemia >40%). Additionally, an effective strategy should increase public awareness of anemia, enabling the public to ensure adequate nutrient intake to maintain bioavailable iron levels and boost factors such as vitamin C.

Limitations

This study has some limitations. First, the overall prediction presented in the model was quite low, suggesting other factors that have not been investigated may have affected the success of the iron supplementation therapy. Second, as we cannot consistently monitor the participants, we may have overestimated the participants' adherence, especially in the pill counting method. There is always a possibility that the participants did not report all the remaining tablets due to the Hawthorne effect. This study cannot obtain the relative change in hemoglobin levels because there were only two hemoglobin measurements (day 0 and day 30).

Moreover, we did not measure the iron levels due to limited access to laboratory facilities in that area. Lastly, we only included six districts in this study due to geographical challenges and the lack of initial data available from all districts in the Teluk Bintuni Regency. Thus, the generalizability of these findings for the entirety of the Teluk Bintuni Regency population is restrained. However, the six districts selected already represent the differences in economics, education, and latitude level in the Teluk Bintuni Regency.

Conclusions

In summary, this study found that ethnicity, adherence to MARS and pill counting methods, and the type of supplementation used were correlated with the success of iron supplementation therapy. The current study found a high prevalence of anemia (53.3%) in the WRA population, with 12.6% having moderate or severe anemia. While iron supplementation continues to be the first line of defense against anemia in many countries, its implementation should be closely monitored. It is not solely dependent on the participants' compliance with supplementation, and ineffective supplementation may also result in other undesirable conditions.

Authors' Contribution

RA, EWS, AAS, and MRAAS participated in the study design. YR contributed to data collection, evaluation, and drafting. RKS and SDA performed data analysis and draft revision. RA has responsibility approval the final manuscript. All authors agreed to the final version of the manuscript and all aspects of the work.

Conflict of Interests

Authors declare that they have no conflict of interests.

Ethical Issues

This study was approved by the Health Research Ethics Committee of Universitas Padjadjaran, Jatinangor, Indonesia (identifier: 172/UN6.KEP/EC/2018). Then, this study was registered in the ISRCTN registry (identifier: ISRCTN96148278). All participants have given informed consent.

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