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A systematic review of iron supplementation's effects on adolescent girls

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ABSTRACT

Background: Anaemia is a nutritional problem that mostly affects adolescent girls around the world and has become a public health problem in many countries. Iron supplementation is one of public health intervention used to prevent adolescents from iron deficiency anaemia. Various countries have widely applied this program to reduce and prevent anaemia in adolescent and pregnant women.

Objectives: Therefore, this literature review will discuss the effects of iron supplementation program on adolescent girls.

Materials and Methods: This study was a systematic literature review of eight articles. These articles were found from scientific journal articles from five databases (Proquest, Science direct, EbscoHost, Pubmed, SAGE). The keywords used are "Iron tablet", "Adolescent" and "Effect". The results were further filtered by the following criteria: last ten years, full text, research article, and English language and Randomized Controlled clinical Trial (RCT) study design.

Results: Our study showed iron supplementation in adolescent girls increased haemoglobin status, serum ferritin and decreased anaemia prevalence.

Conclusion: Initiatives for iron supplementation programs among adolescent girls are necessary to reduce iron deficiency anaemia.

Keywords: *Adolescent; Good Health; Iron; Nutrition; Well-being*

BACKGROUND

Women of reproductive age are at risk for iron deficiency anaemia, which is a public health problem, including adolescents. Anaemia afflicted 613.2 million women of reproductive age, and 32.5% were non-pregnant women, including adolescents, in 2016. An increase of cases occurred from 30.3% in 2012 to 32.8% in 2016.[1] The worldwide prevalence of anaemia in women of reproductive age in 2019 was 29.9%.[2] This frequency was 29.6% in reproductive-age non-pregnant women and 36.5% in pregnant women. Since 2000, the incidence of anaemia among pregnant women has considerably decreased, although the frequency of anaemia in women of reproductive age overall has remained consistent. Estimating the total burden of anaemia due to severity and underlying causes allowed for more accurate target of treatments to the highest-burden sites and the factors contributing the most to total prevalence.[3] Adequate actions must be implemented to achieve a 50% decrease in anaemia in women of reproductive age.

The risk of iron deficiency anaemia among adolescent girls could be enourmous. Anaemia was shown to be associated with cellular stress, as evidenced by greater serum anti-HSP 27 levels indicating cellular stress such as inflammation and oxidative damage.[4] It could be the cause of the scores of adolescent girls with anaemia were considerably lower than those of girls without anaemia especially on subscales testing memory, inhibitory control, selective attention, decision-making, and planning. Researchers also discovered that anaemia adolescents have a greater risk of low birth weight, prematurity, perinatal and young mother mortality.[5] This problem also becomes a national burden because negative consequences of impaired mental development will affect human capital formation.[5]

One of the recommendations from WHO regarding intervention for girls and preventing anemia is early intervention in adolescents to prevent iron deficiency anemia, especially in areas with high teenage birth rates and early marriage.[5] This is done by giving iron supplements. Iron supplements are generally given in the form of tablets.[6] Supplementation is given in the form of tablets containing 60 mg of elemental iron and 2.8 mg of folic acid once a week for three consecutive months followed by three empty months and repeated again in the following month. WHO also added that if possible, supplementation can be provided throughout the learning year.[7] In Indonesia, iron tablet is given to all adolescent girls aged 12-18 years with a composition

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of 60 mg elemental iron and 0.4 mg folic acid. This supplement is given once per week throughout the year which is carried out simultaneously at school according to the time determined by each institution.[8]

However, some studies show that the compliance rate of iron tablet consumption among adolescents is still challenging.[9,10] Compliance is a person's behavior towards something that is done continuously and constantly. A wrong perception of the behaviour can lead to the formation of the desired behaviour. Adolescent perception of iron tablet consumption begins with adequate knowledge of the advantages and risks of iron tablets. Previous research has shown that many barriers came from personal factor such as fear of iron tablet's side effect, unaware of positive effect of iron tablet, missperception of iron tablet as contraception and lack of knowledge about iron tablet.[11] So far, more research has addressed iron tablet supplementation among pregnant women, and it is still limited to discussing iron tablets among adolescents. Therefore, the systematic review needs to address iron supplementation's effects on adolescent girls so it will provide more information and improve knowledge of adolescent girls about iron tablet and enhance the compliance of consuming iron tablet.

MATERIALS AND METHODS

This paper was a systematic review that uses the PRISMA declaration and checklist for recommended reporting elements for systematic reviews and meta-analyses. The question of the study was: What is the effect of using iron supplementation in adolescent girls?

Literature searches use five databases (Proquest, Science direct, EbscoHost, Pubmed, SAGE) as shown in Figure 1. The keywords used are "Iron tablet", "Adolescent" and "Effect". The results were further filtered by the following criteria: last ten years, full text, research article, and English language and Randomized Controlled clinical Trial (RCT) study design. Figure 1 depicts the PRISMA flowchart diagram of the research inclusion procedure.

The initial search was done from five electronic databases. A total of 1045 results were found based on the keyword. Filtration for the articles is articles within five years (2016 – 2022), with full accessed articles, full text, and English language. After filtration and eliminating duplication, 501 reports were obtained for screening. The screening was done by reading abstracts and adjusting to research questions. A total of 454 articles were excluded because they did not meet the criteria. Therefore, eight articles were included in this study. A flow diagram of the literature search is presented in Figure 1.

Interventional Randomized Controlled Trials (RCT) studies that met the following inclusion criteria were included. Inclusion criterias were based on PICO (Population, Intervention, Comparison, and Outcome).[12] P: Adolescents participated in the study with age range of 10-19 years old, I: Iron pills were employed as an intervention in the studies with or without combination with other nutrients such as folic acid, C: Studies that examine the impact of interventions on the effect of iron tablets within the group or comparison of intervention groups, and O: Studies that assess the impact of the iron tablet especially in hemoglobin levels and serum ferritin. We omitted studies published before 2016 and those with a non-adolescent population. HTHS is in charge of locating papers, and eligibility judgments are made during restricted meetings with LAS and IN. Decisions are made collectively.

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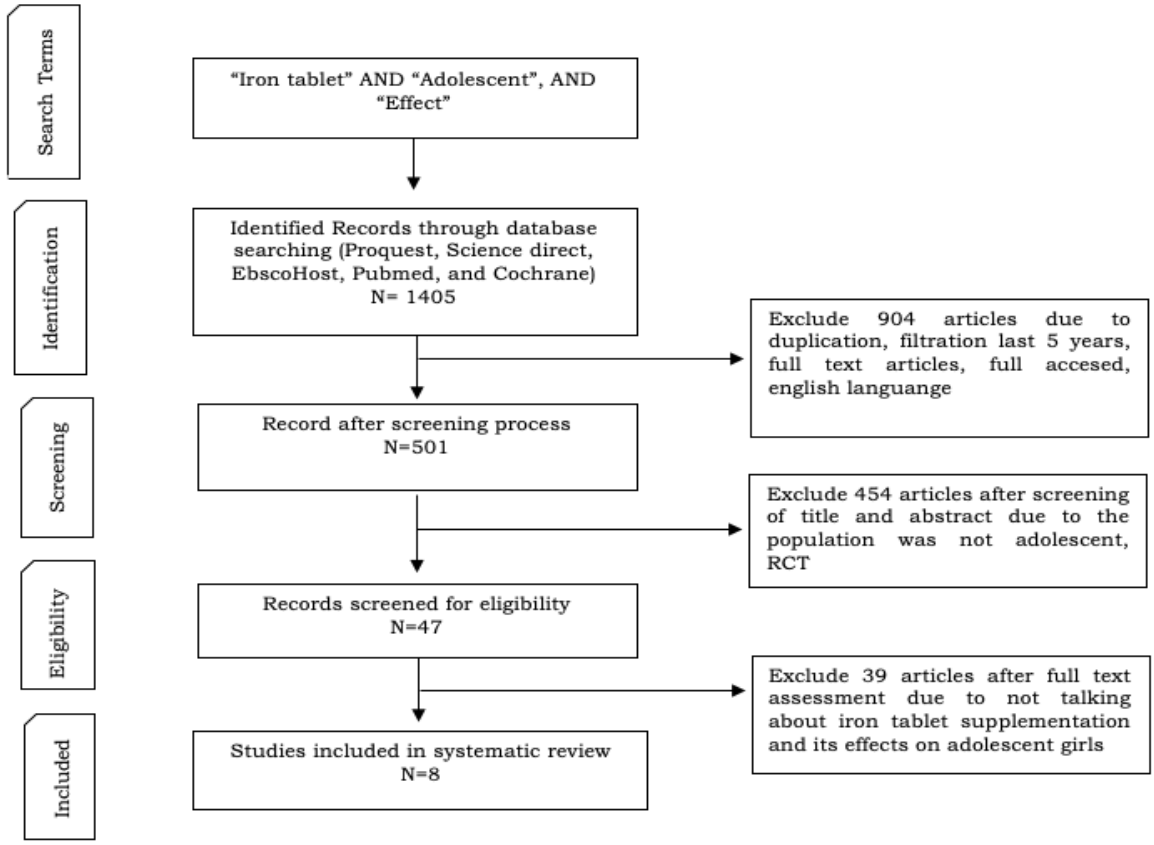

Figure 1. Literature Searching and Selection with PRISMA Flow Diagram

RESULTS

Studies Characteristics

Table 1 shows the general study features of the eight papers in this investigation, which shows publishing years, research site, and the research duration. The results discovered that research related to the effects of iron supplementation was at least carried out after being provided for one month, and there were additional studies that looked at the results after being given for more than a year.

The effect of iron supplementation on adolescents

Table 2 shows the effects of oral iron supplementation in adolescents. Adolescent girls who receive iron supplements benefit from higher haemoglobin and ferritin levels as well as the prevention of anaemia. The provision of iron supplementation requires special attention in adolescents living in malaria-prone areas and adolescents with subclinical inflammation. Four of the eight articles demonstrated the same thing: an increase in serum ferritin and Hb levels, indicating a reduction in anaemia prevalence, after iron supplementation for at least two months.[13] These findings is different with one study conducted by Gies *et al.* that found no significant increase in serum ferritin after 18 months of treatment.[14] This distinction is due to the fact that the population group analyzed by Gies *et al*. is lived in an area with high malaria transmission rates. According to this study, weekly iron supplementation in a malaria-transmission area did not improve iron status or reduce anemia in young, mostly adolescent menstrual women. Iron absorption investigations are required to evaluate whether chronic malaria affects iron consumption. These findings are relevant to malaria-endemic areas with high incidence of silent teenage malaria, as baseline characteristics were similar to those seen in low-income, rural sub-Saharan Africa. In contrast, a study conducted by Brabin *et al.* found that iron supplementation could enhance body iron storage while also increasing the risk of malaria during the rainy season.[15] Other result found that iron supplementation paired with vitamin A improved iron supplementation effectiveness and increased Hb and serum ferritin levels after 12 weeks of intervention in subclinical inflammation conditions.[16]

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Table 1. General Study Characteristics of Included Studies (n=8)

Categories	*Number of Studies*
Publication Year	
2017	1
2018	2
2019	1
2020	2
2021	2
Time of intervention/observation	
1-3 months	2
>3- 6 months	2
>6 months – 1 year	2
>1 year	2
Site of research	
Palestine	1
Burkina Faso	3
India	2
Ethiopia	1
Myanmar	1

DISCUSSION

In the current study, experimental groups receiving an iron supplement had higher serum ferritin and haemoglobin levels. Our results demonstrate that iron supplementation increases the body's levels of ferritin and haemoglobin.[15–17,21] It is essential for adolescent girls who are still in their menstruation and full of activity[21] to take iron supplements to increase haemoglobin levels. In addition to using iron tablets, food consumption also can increase haemoglobin levels. For example, the consumption of two ambon bananas (100 g) every day for a month with an average increase of 0.39 g/dL.[22] Consuming ten pieces of Ajwa date fruit can increase haemoglobin with an average of 0.357 g/dL.[23] This is also in line with our findings that demonstrate Hb and ferritin levels increase in the subjects who received nutrition education. Therefore, education about nutrition is highly recommended, along with the provision of iron tablets to maintain the increase in Hb levels.[17] India is one country that has successfully reduced the prevalence of anemia. A weekly iron-folate supplementation program for adolescent girls was implemented in 52 districts across 13 states. This initiative targets females aged 10 to 19 years old, both in and out of school. This program's evaluation revealed a 24% reduction in anemia prevalence after one year of implementation. Weekly iron supplementation for over 1.2 million adolescent girls in Gujarat reduced anemia prevalence from 74.2% to 53.5% in one year, with an estimated compliance rate of more than 90%.[24] This study identified several important factors in achieving compliance in adolescent girls above 85%, including adolescents' knowledge of the consequences of anemia, the benefits of iron supplementation, having shared days to take iron tablets, ongoing monitoring, service packages including counseling, and support to improve young women's motivation and interests.

Due to their inexpensive cost and good absorption, ferrous sulfate and ferrous gluconate are commonly used as oral iron supplements. Nausea and abdominal pain are common side effects of iron absorption when administered on an empty stomach.[25] Iron therapy successfully treated pica, cheilitis, and RLS (restless limb syndrome). 92.3% of women improved their nails, while 84.2% improved their hair loss. Iron therapy was also associated with improved executive attention and working memory function.[26] Outcomes of iron supplements in adolescents showed a decline in the incidence of iron deficiency anaemia.[27] Haemoglobin deficiency below normal limits (women 12 g/dL) can usually indicate anaemia despite differences between global values set by WHO and based on national surveys of certain countries.[28] Iron deficiency anaemia occurs when the body lacks iron. It can happen due to an increased iron requirement that is not balanced with adequate iron intake, bleeding that causes a lot of blood loss, and iron, a condition in which the intestines cannot absorb iron optimally.[29] In some countries, adolescents who live in low socio-economic areas need to obtain much attention.[30] Iron supplementation might contribute in preventing iron deficiency anaemia among adolescent girls that live in low socio-economic areas. Besides iron supplementation, health education was also important in preventing anaemia among adolescent girls. Research conducted by Alami et al. (2019) on Iranian adolescents shows that interventions in the form of education around iron consumption can increase knowledge

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and intention to consume iron.[31] Previous research investigating the variables influencing iron intake revealed a substantial link between knowledge and the intention to take iron supplements.[32]

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Many advantages are offered by consuming iron tablets, on the other hand, there are barriers for adolescents in consuming iron tablets independently. One deterrence in adolescents' adherence to iron tablets is its side effects. Some unwanted effects of iron tablets are dizziness, continuous hunger, nausea, vomiting, abdominal pain, headaches, big black water, and odour. These side effects are also found in the first week of iron tablet consumption and will decrease in the following weeks.[33] It is necessary to ensure that adolescents can consume iron tablets independently. Adolescents did not take iron supplements not only because of knowledge or the benefits they perceived. Adolescent girls' propensity to use iron supplements is influenced by perceived self-efficacy.[34]

The present study also shows that the administration of iron supplementation can increase iron deposits in the body, increasing the risk of malaria, especially in the rainy season.[15] On the other hand, studies have shown that when regular malaria preventive or management services are provided, iron therapy does not raise the risk of clinical malaria.[35] Giving iron supplements in conditions with subclinical inflammation can also affect the expected results, increasing iron deposits. In adolescents with Subclinical Inflammation (SCI), oral iron administration should be followed by the administration of vitamin A. It shows better results when compared to giving iron itself without vitamin A.[16]

This research found publication articles from different countries and was not focused on one country or continent that had the same characteristics, so other factors that lead to different results might be happened according to some circumstances of site research.

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Table 2. Characteristics of the Included RCT Studies of Iron Supplementation with Adolescents (n=8)

Ref.	*Sample size*	*Study design*	*Baseline*			*Intervention*			*Summary of findings*
			Hb levels	*Ferritin levels*	*Others*	*Doses*	*Freq*	*Measurement*	
Jalambo et al., 2018 [17]	131 iron-deficient female adolescents (15-19 yo)	RCT	Group A: 11.52 g/dL Group B: 11.45 g/dL Group C: 11.73 g/dL	Group A: 9.92 μg/dL Group B: 9.19 μg/dL Group C: 9.70 μg/dL	MDA: Group A:90.14 Pmol/ml Group B:91.5 Pmol/ml Group C: 96.3 Pmol/ml	Group A: 200 mg of ferrous fumarate weekly. Group B: iron supplements, and dietary instruction. Group C (control): no intervention.	Weekly	Three months after intervention and three months after the intervention ended	Three mo after intervention: Group A: Hb levels ↑; Ferritin levels ↑; MDA levels ↑ Group B: Hb levels ↑; Ferritin levels ↑; MDA levels ↑ Group C: Hb levels ↔; Ferritin levels ↑; MDA levels ↑ Three mo after the intervention ended: Group A: Hb, Ferritin, MDA ↓ Group B: Hb ↑; Ferritin ↑; MDA ↓ Group C: Hb, ferritin, MDA ↔
Htet et al, 2019 [16]	402 school girls (15-17 yo)	RCT	Group 1: 8.9 ± 1.3 g/dL Group 2: 8.9 ± 1.1 g/dL Group 3: 8.8 ± 1.1 g/dL Group 4: 8.8 ± 1.2 g/dL	Group 1: 29.9 ± 2.5 μg/dL Group 2: 33.4 ± 2.5 μg/dL Group 3: 31.4 ± 2.4 μg/dL Group 4: 25.5 ± 3.1 μg/dL	CRP: Group 1: 0.73 ± 2.07 mg/dL Group 2: 0.96 ± 3.32 mg/dL Group 3: 1.38 ± 6.08 mg/dL Group 4: 0.47 ± 0.87 mg/dL	Group 1: Folic acid (2.5 mg of folate). Group 2: Vitamin A (15000 IU of vitamin A) Group 3: Iron and folic acid (IFA) (60 mg elemental iron and folate) Group 4: iron, folic acid, and Vit A	Weekly	The change in Hb, serum ferritin and body iron store were compared among the four treatments after 12 weeks after intervention.	Serum ferritin ↑ in the IFA and IFA + vit A groups when compared to individuals who did not have subclinical inflammation (SCI). There was an association between vitamin A and SCI on Hb changes. Those who were given vitamin A survived better when there was SCI. Inflammation was linked to a decrease in iron supplementation efficiency, but vitamin A increased iron supplementation effectiveness in the presence of SCI.

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Table 2. Characteristics of the Included RCT Studies of Iron Supplementation with Adolescents (n=8) (Lanjutan…)

Ref.	*Sample size*	*Study design*	*Baseline*			*Intervention*			*Summary of findings*
			Hb levels	*Ferritin levels*	*Others*	*Doses*	*Freq*	*Measurement*	
Brabin et al., 2020 [15]	1084 adolescent girls (16-18 yo)	RCT	-	41.2 µg/dL	Median adjusted body iron stores (BIS): 2.8-7.1 (5.3) mg/kg	60 mg ferrous gluconate with 2.8 mg folic acid	Weekly	17-26 weeks. Iron biomarkers and malaria were measured.	After controlling for the use of bed nets, age, menarche, and body mass index, higher baseline iron reserves suggested an increased risk of malaria in the next rainy season (OR 1.18 (95 percent CI 1.05, 1.34, p = 0.007)).
Handiso et al., 2021 [18]	226 adolescent girls (10–19 yo)	RCT	Group 1: 13.3±1.4 g/dl Group 2: 13.1 ± 0.7 g/dl	Group 1: 58.5 ± 35.2 µg/dL Group 2: 61.1 ± 39.1 µg/dL	Serum folate: Group 1: 10.2 ± 4.3 ng/ml Group 2: 11.2 ± 4.6 ng/ml CRP: Group 1: 0.66 ± 1.3 µg/l Group 2: 0.56±1.2 µg/l	Group 1: 60 mg elemental iron and 0.4 mg folic acid supplementation Group 2: control (receive nothing)	Weekly	After three months of supplementation	Group 1: Hb ↑, SF ↑, Serum Folate ↑, CRP ↑ Group 2: Hb ↔, SF ↔, serum folate ↔, CRP ↑
Gupta et al, 2021 [13]	769 adolescent girls (12-19 yo)	RCT	Group 1: 10.3 ± 0.9 g/dL Group 2: 10.5 ± 0.8 g/dL	Group 1: 29.6 ± 35.2 µg/dL Group 2: 35.1 ± 35.1 µg/dL	Serum vit B12: Group 1: 256.3 ± 73.5 pg/ml Group 2: 226.3±77.3 pg/ml	Group 1: IFA (iron 60 mg, folic acid 500 mcg + Vit B12 1000 mcg Group 2: IFA + Placebo	Daily	90 days of supplementation	Group 1: Hb levels ↑, Serum Ferritin ↑, serum vitamin B 12 ↑ Group 2: Hb levels ↑, Serum Ferritin ↑, serum vitamin B 12 ↓

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Table 2. Characteristics of the Included RCT Studies of Iron Supplementation with Adolescents (n=8) (Lanjutan…)

Ref.	*Sample size*	*Study design*	*Baseline*			*Intervention*			*Summary of findings*
			Hb levels	*Ferritin levels*	*Others*	*Doses*	*Freq*	*Measurement*	
Gies et al, 2018 [14]	1973 adolescent girls (15-24 yo)	RCT	-	Group 1: 49.0 (28.0–79.8) μg/dL Group 2: 50.0 (27.0–81.0) μg/dL	CRP: Group 1: 0.58 (0.23–1.43) mg/L Group 2: 0.50 (0.18–1.29) mg/L	Group 1: 60 mg elemental iron, 479 mg gluconate and folic acid 2.8 mg Group 2: folic acid 2.8 mg	Weekly	18 months of supplementation	Comparison between groups 1 and 2: Hb levels: ↔ Serum Ferritin: ↔
Singh, et al., 2020 [19]	210 adolescent school girls (15-18 yo)	RCT	-	-	Prevalence anaemia in group 1 decreased from 93.3% to 38.6%. Prevalence anaemia in group 2 decreased from 100% to 74.0%.	Group 1: WIFAS + health education once a month. Group 2: WIFAS	Weekly	Six months	After six months, the prevalence of anaemia ↓ in group 1.
Brabin et al, 2017 [20]	1549 non-pregnant adolescent girls (15-24 yo)	RCT	-	-	Iron deficient: Group 1: 84 (11.1) Group 2: 100 (13.0) Bacterial vaginosis Nugent>6: Group 1: 80 (13.0) Group 2: 68 (10.8)	Group 1: iron (ferrous gluconate 60 mg) + folic acid 2.8 mg Group 2: folic acid 2.8 mg	Weekly	18 months	BV and *T. vaginalis* prevalence and microbiota profiles between groups 1 and 2 after intervention: ↔

Ref: Reference; Yo: years old; ↑: significant increase; ↓: significant decrease; ↔ no change; freq: frequency; BV: Bacterial vaginosis; *T.vaginalis*: *Trichomonas vaginalis*; WIFAS: weekly iron-folic acid supplementation; CRP: C-Reactive Protein; Hb: haemoglobin; MDA: malonyl dialdehyde; SCI: sub-clinical inflammation; Hb: haemoglobin; SF: Serum Ferritin

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CONCLUSIONS

In the RCT study, the provision of iron tablet supplementation increased haemoglobin and ferritin levels in the body, ultimately reducing the risk of iron deficiency anaemia among adolescent girls. Therefore, the iron supplementation program among adolescent girls is necessary to prevent iron deficiency anaemia. Efforts to increase knowledge and adherence regarding Fe tablets are necessary to reduce iron deficiency anemia in adolescents.

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