Effects of Iron Therapy on the reduction of anemia among women of reproductive age in developing countries: A protocol for systematic review and Meta-analysis

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Protocol

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Abstract

Background

Iron deficiency anemia is a major public health issue among women of reproductive age (WRA), as it leads to high maternal and infant morbidity and mortality. The WHO recommends the distribution of iron supplements to all women in populations in which the prevalence of anemia (in women) exceeds 20%. Interventional studies have been carried out in developing countries regarding the efficacy and safety of iron in reducing anemia among women of reproductive age. However, the findings from randomized controlled trials have not been systematically synthesized. Therefore, we performed a systematic review and meta-analysis of RCTs to both qualitatively and quantitatively assess the evidence for the efficacy and effectiveness of iron as an intervention for reducing anemia among women of reproductive age in developing countries.

Methods

This review and meta-analysis will focus on assessing the efficacy and effectiveness of iron as an intervention for reducing anemia among women of reproductive age. PubMed, Google Scholar, and Science Direct will be explored using a detailed search strategy. A study will be considered eligible if it is a randomized controlled trial determining the efficacy and effectiveness of iron in anemia reduction among WRA (15-49 years) in developing countries and published in the English language in a peer-reviewed local or international journal from 2000 to 2020. We will perform a meta-analysis to measure the effect of individual studies as well as the pooled effect of all studies by generating forest plots. Heterogeneity will be assessed using I^2 statistics and a funnel plot will be developed to assess the publication bias.

Discussion

This systematic review will provide an opportunity to synthesize and critically appraise the findings from individual studies on the efficacy and effectiveness of iron as an intervention for reducing anemia among women of reproductive age to generate a comprehensive summary. These aggregated findings, in turn, can guide clinical practice and help clinicians, researchers and policymakers make evidence-based decisions to address this pressing health concern among women of reproductive age residing in developing countries. The findings of the review will be disseminated through presentations and peer-reviewed publications.

Background

Anemia is a major public health issue among women of reproductive age (WRA), as it leads to high maternal and infant morbidity and mortality (1). It occurs when the number and size of red blood cells or the hemoglobin (Hb) concentration fall below an established cut-off value, consequently impairing the capacity of the blood to transport oxygen to the body (2, 3).

The World Health Organization (WHO) defines anemia as Hb levels of <12.0 g/dL among women of reproductive age (4).

The WHO has recognized anemia as a global health concern with serious consequences for mothers and their children(5). More specifically, anemia can lead to adverse outcomes both for WRA and their children (6). The consequences of anemia vary according to the type and severity of anemia among WRA (7, 8). Several studies have shown that anemia among pregnant women can result in poor maternal and fetal outcomes such as abortion, intrauterine growth retardation, post-partum hemorrhage, stillbirths, low-birth-weight, prematurity, and perinatal mortality (9–12). For instance, a review of observational studies found a linear association between maternal anemia and maternal mortality, with each 10 g/L increase in maternal hemoglobin associated with a 29% reduction in maternal mortality (13). Likewise, findings from a systematic review revealed that 25% of low birth weight babies, 44% of preterm deliveries, and 21% of perinatal mortality are attributable to anemia during pregnancy in low- and middle-income countries (LMICs) (14). Furthermore, a meta-analysis showed an increased risk of preterm birth among women who experienced anemia in the first trimester of pregnancy with an overall odds ratio of 1.32 (15). Most recently, a study based on the WHO multi-country survey demonstrated that severe anemia is associated with a two-fold increase in the risk of maternal death (16).

Although anemia has been shown to affect women in both high- and low- and middle-income countries, the major burden of anemia is found in LMICs (17, 18). More specifically, anemia affects nearly two-thirds of WRA in LMICs (19). According to the WHO, about half a billion WRA are anemic worldwide, with a higher burden of anemia in South-East Asia (41.9%), followed by African and Eastern Mediterranean regions (20). For example, studies from India show that the prevalence of anemia among WRA ranges from 50% to 90% across different geographic areas of India (21–23). Likewise, community-based cross-sectional studies conducted in Ethiopia demonstrate that 34.5% to 56.8% of the WRA are suffering from anemia across different regions of Ethiopia (24–26). Similarly, a study conducted in Uganda found 63.1% of women to be anemic, with a similar study from Bangladesh revealing more than a third of women to be anemic (27). In addition, estimates in high-risk populations suggest that total anemia prevalence may be as high as 50% to 80% in developing countries, with as many as 10% to 20% having moderate to severe anemia (28). Although multiple interventions have shown to reduce the prevalence of anemia worldwide by 12% between 1992 and 2011, these efforts did not have a similar impact in LMICs (29).

The existing literature highlights that multiple factors, such as smokeless tobacco, infectious and chronic diseases, dietary inadequacy including a lack of intake of food sources rich in iron, folic acid, and vitamin B12 can cause anemia among WRA, mainly in developing countries (30–32). In addition, studies conducted in different developing countries have shown that normal physiological changes of pregnancy, hemoglobinopathies, malaria, HIV, and hookworm infestation can also contribute to anemia among WRA in these countries (31, 33, 34). Additional factors that predispose WRA to anemia include differences in lifestyles, socio-demographic factors, hygiene conditions, and genetic susceptibility (35, 36).

Iron deficiency, in particular, has long been considered a major cause of anemia among WRA as they are at high risk of iron deficiency and iron-deficiency anemia due to menstrual blood losses(37). It has been presumed that iron deficiency contributes to 50% of all anemia among women of reproductive age mainly in South Asian and African regions (38, 39). The WHO recommends the distribution of iron supplements to all women in populations in which the prevalence of anemia (in women) exceeds 20% (40). Basic and applied sciences have made major contributions in recent decades to understanding the effects of iron-deficiency anemia, and have made recommendations for remedial and preventive actions. In this regard, multiple epidemiological studies have been done to assess the effect of iron in the reduction of anemia among women of reproductive age in developing countries. Moreover, interventional studies have been carried out in developing countries regarding the efficacy and effectiveness of iron in reducing anemia among women of reproductive age. However, findings from randomized controlled trials have neither been systematically synthesized nor have they measured a final effect size of iron as an intervention by pooling results from all randomized controlled trials (RCTs). This limits the capacity of primary and specialist clinicians and policymakers in developing countries to anticipate potential benefits when considering strategies to prevent and treat iron deficiency. Therefore, we will perform a systematic review and meta-analysis of RCTs to both qualitatively and quantitatively assess the evidence for the safety and effectiveness of iron as an intervention for reducing anemia among women of reproductive age in developing countries.

Material And Methods

This protocol has been designed and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocols (PRISMA-P) checklist (41) (Figure 1).

The review will focus on assessing the evidence for the safety and effectiveness of iron as an intervention for reducing anemia among women of reproductive age in developing countries. Additionally, this review will provide evidence for clinicians and policymakers to prescribe iron as an intervention for WRA in their respective settings. This, in turn, will help to make inferences about the evidence and set recommendations to address the high burden of anemia among women of resource-poor settings.

Eligibility Criteria

We will undertake a systematic review and meta-analysis on the effects of iron as an intervention for reducing anemia among women of reproductive age mainly in developing countries. The criteria used to define a 'developing country' are based on the World Bank's 2018-guidelines of country classification. Overall, the eligibility criteria are grouped into five categories including population, intervention, comparison, outcome, and settings, etc. (Table 1). More specifically, a study will be considered eligible for inclusion if it is primarily a randomized controlled trial determining the efficacy or effectiveness of iron in reducing anemia among WRA (15–49 years) in developing countries and published in the English language in a peer-reviewed local or international journal from 2000 to 2020. An inclusion/exclusion screening form is given in Table 2.

Primary outcome

The primary outcome of the review is anemia and we will include studies that have used hemoglobin (Hb) levels (grams per deciliter (g/dL)) in the blood to classify a woman as anemic. More specifically, we will include the studies that have used the World Health Organization (WHO) cut-offs of hemoglobin level <12.0 g/dL or Hct <36% and <11.0 g/dL or Hct <33.0% respectively to classify a non-pregnant and pregnant woman as anemic (52).

Information sources and search strategy

An electronic systematic literature search will be carried out on the effects of iron as an intervention for reducing anemia among women of reproductive age in developing countries. Although there are several databases to search for articles on the given research topic, we will search three large electronic databases including PubMed, Google Scholar, and Science Direct for the current systematic review. These databases will be explored using a detailed search strategy including search terms or combinations. In addition, within these databases, we will include studies from relevant journals such as The Lancet, Blood Journal, British Medical Journal, Gastroenterology Journal, Nature, PLOS-Medicine, Journal of Clinical and Diagnostic Research, The New England Journal of Medicine, Nature & Nature Medicine, Clinical Infectious Diseases and Annals of Internal Medicine. Moreover, the reference lists of the included records will also be searched to identify relevant articles.

The databases will be searched by two researchers independently. The search strategy will be piloted to ensure sufficient specificity and sensitivity. More specifically, articles will be searched using a combination of search terms set out for the defined research question. The preliminary search strategy is illustrated in Table 3. These search items are grouped according to the PICOS criteria (42): 1) Population (WRA), 2) Intervention /Exposure (Iron therapy in any form), 3) Comparison group (Women who are given intervention other than iron or placebo), 4) Outcome (anemia), and 5) Settings (developing countries). We have identified four major concepts (anemia, WRA, iron, and developing countries) and their synonyms such as low hemoglobin/hematocrit level (anemia), married women/married pregnant women/ married non-pregnant women (WRA), iron/iron supplements/iron therapy/iron regimen(Intervention) and low-middle- income countries/low-income countries/less developed countries (developing countries). In addition, we will also consider using different spellings of major concepts such as anemia vs anaemia and hemoglobin vs haemoglobin, etc. to capture relevant articles. This will be followed by combining the major concepts using combinations (AND, OR) germane to the research question. Moreover, we will use truncation (*) to identify additional research articles with the same root word. Additionally, indexed keywords in the Medical Subject Headings (MeSH) will be used to ensure uniform search terms.

As an example, to capture relevant articles in a given database, the following simple search terms can be used independently or in combination:

Example:Iron supplements OR Iron therapy OR Iron tablets [MeSH Terms] AND (anemia OR iron deficiency anemia*) AND (women of reproductive age OR married* OR pregnant*) AND (developing*

countries) (Table 3).

We will also apply search limits or filters on publication year (2000–2020), language (English), age group (15–49 years), gender (females) and type of studies (RCTs) to include eligible articles in the search.

Study selection

Citation management system (Endnote software) will be used to manage records exported from all the electronic databases(43). In the first step, all the studies will be screened by study titles using the Endnote software. The shortlisted studies will then be screened by study abstracts. Lastly, the full text of selected studies will be retrieved and screened against the eligibility criteria. To ensure the reliability of screening articles among the two reviewers, a pre-defined screening form will be developed and pilot testing will be conducted as per the eligibility criteria. Both reviewers will describe outcome measures after reviewing studies to verify the relevance of the articles. Strong justifications for excluding studies will be provided by each reviewer. Any disagreement between the two reviewers will be resolved by a third reviewer in a consensus meeting. The third reviewer will be consulted to make the final decision about whether the study meets the eligibility criteria for inclusion. The PRISMA flow diagram will be used to report the study selection process.

Data collection process

A customized data extraction sheet will be filled by two independent reviewers for the eligible studies. Data extraction tables of both reviewers will be matched to ensure that all key findings are included in the systematic review. A third evaluator will be involved, if discordant information is observed during the data extraction process. The data extraction sheet will be pilot tested before initiating the data extraction process. Alongside, existing studies on this research area have been reviewed to determine items for the data extraction form. The items included in the preliminary data extraction form include the title of the article, author, publication date, country of study, date of extraction, reviewer name, purpose/aim of the study, study type, study population, iron as an intervention, duration of follow-up, type of intervention, randomization method, whether or not blinding was done and study limitations. The summary of included studies on the effects of iron in reducing anemia among WRA will also be provided in the main results paper.

Assessment of risk of bias in included studies.

Risk of bias will be assessed by 2 authors independently using the Cochrane risk-of-bias tool, which addresses selection, performance, attrition, detection, and reporting bias through evaluation of reported sequence generation, allocation concealment, blinding of participants and personnel, incomplete outcome data, selective outcome reporting, and other possible sources(44). Studies will be considered at a high overall risk of bias if randomization or allocation concealment is judged as being at a high (or

unclear) risk of bias or in the absence of blinding or with high or imbalanced attrition rates. Studies not meeting this criteria will be considered at a low overall risk of bias.

Synthesis of included studies

First, the findings of the review will be synthesized narratively. Initially, we will perform a descriptive analysis of all the final included studies to record their main characteristics such as study title, authors, publication year, study aim, study methods, sampling strategy, characteristics of study participants, study population, iron as an intervention, duration of follow-up, type of intervention, and randomization method. Firstly, two independent reviewers will read each included study multiple times to extract data and group related results. Following this, the reviewers will record analytical interpretations of findings to capture emerging themes. Finally, they will highlight the effects of iron in reducing anemia among WRA in developing countries.

Statistical Analysis

Open Meta[analyst] software will be used to perform a meta-analysis of all eligible studies using mean and standard deviation for hemoglobin as an outcome from different studies. We will use the standardized mean difference (SMD) with the 95% CI to express differences in mean for hemoglobin. An inverse variance statistical method and random-effect (or fixed-effect) analysis will be used for this meta-analysis to account for differences in the conduct of some studies (sample size, outcome assessment, and tools to measure the outcomes) that will be included in the meta-analysis. Heterogeneity will be assessed using the I^2 statistic and significant heterogeneity will be considered to exist when I^2 exceeds 50%. Forest plots will be developed to measure the individual and pooled effects of studies and to assess statistical heterogeneity. A value of $p < 0.05$ will be considered statistically significant. Moreover, funnel plots will be examined for asymmetry to identify publication bias.

Discussion

A more comprehensive understanding of the efficacy and effectiveness of iron in reducing anemia is required to address the burden of anemia among WRA in developing countries. This protocol will lead to a systematic review and meta-analysis, which synthesizes evidence on the effects of iron in reducing anemia in both urban and rural communities of developing countries in Asia and Africa. Systematic review and meta-analysis findings will be made publicly available. This systematic review and meta-analysis will provide an opportunity to synthesize and critically appraise the findings from individual studies on the effects (efficacy and effectiveness) of iron in reducing anemia among WRA to generate a comprehensive summary. These aggregated findings, in turn, can guide clinical practice and help policymakers make evidence-based decisions to address the problem of anemia among women of reproductive age in developing countries. The results of the review will be disseminated through presentations and peer-reviewed publications.

Abbreviations

HB: hemoglobin

PICOS: Population, Intervention, Comparison, Outcome, and setting

PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols

WHO: World Health Organization

WRA: Women of reproductive Age

Declarations

Consent for publication

Not applicable

Availability of data and materials

Materials described in this paper pertain to the protocol only and there are no raw data reported. The studies will be retrieved and analyzed and can be made available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

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Authors' contributions

The study was conceptualized by SuA & SaA. Dr. SuA prepared the first draft of the manuscript and SaA edited the draft and supervised the reviewers to carry out the review. AA and AAA carried out the review of the articles, compiled all the data, reviewed the manuscript, and provided feedback. FR reviewed the manuscript and approved it. All authors have contributed to this manuscript, and reviewed and approved the final version of the paper.

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Tables

Table 1: Eligibility criteria according to the PICOS framework		
Attribute	Inclusion Criteria	Exclusion Criteria
Population	<p>All studies including women of reproductive age from 15 to 49 years of age.</p> <p>Studies involving pregnant or non-pregnant women and married or non-married women of reproductive age from 15 to 49 years of age.</p>	<p>Studies involving children or elderly under the age of 15 or over the age of 49 years.</p> <p>Studies focused on men of any age.</p>
Intervention	All interventional (experimental) studies that have measured the effect of iron therapy on the reduction of anemia.	Studies that have measured the impact of any other intervention (other than iron) on anemia.
Comparison	The comparison group will be women who are given intervention other than iron or placebo.	Not applicable
Outcome	Anemia is measured objectively and defined as Hb < 12.0 g/dl or Hct <36% among non-pregnant women, and Hb <11.0 g/dl or Hct <33.0% among pregnant women.	Studies that have measured outcomes other than anemia such as nutritional deficiencies, food insecurity, etc as a proxy indicator of anemia.
Setting	All developing countries as defined by the World Bank's 2018-guidelines of country classification.	Studies conducted in the developed countries as defined by the World Bank's 2018-guidelines of country classification.
Study Designs	Intervention Studies including both randomized and non-randomized controlled trials.	Non-experiment observational quantitative studies (cross-sectional, case-control, cohort), pre- and post-test designs, commentaries, editorials, symposium proceedings, systematic reviews, secondary articles, and qualitative studies.
Language	Studies available in the English Language.	Studies that are not available in English translation.
Time period	Studies published between January 2000 to December 2020 to cover a wide range of recently published literature.	Studies published before January 2000.
Type of journal	Studies published in peer-reviewed local and international journals	Studies published in non-peer reviewed journals

Table 2: Inclusion and Exclusion screening form			
Study Characteristics			Page/ Para/ Figure #
Type of study (Interventional studies)	c Observational study <ul style="list-style-type: none"> c Case-control c Cross-sectional c Cohort 	c Interventional study <ul style="list-style-type: none"> c Randomized controlled trial c Quasi-experimental study c Pre-post design 	
	c Qualitative study <ul style="list-style-type: none"> Exploratory Descriptive Ethnography other 	c Other design (specify):	
	<i>Does the study design meet the criteria for inclusion?</i> Yes c No c à Exclude Unclear c		
Study Participants (Studies involving women of reproductive age 15-49 years)	Describe the participants included:		
	Are participants defined as women of reproductive age from 15-49 years?	Yes c No c Unclear c Details:	
	How is the age or gender defined?	Details: Specific age group and gender (e.g. men / women):	
	<i>Do the participants meet the criteria for inclusion?</i>	Yes c No c à Exclude Unclear c	
Study setting: Developing countries Follow the list of all developing countries of Asia and Africa based on World bank definition of 2018	Is the study conducted in developing countries?	Yes c No c à Exclude Unclear c	

		Specify the region: -----	
		Specify the country :-----	
Intervention (Studies will be included that have measured the efficacy and effectiveness of iron)	Intervention		
	<i>Does the study measure the efficacy and effectiveness of iron in reducing anemia ?</i>	Yes c No c àExclude Unclear c	
	<i>Does the study measure the effects of iron (in any form) in reducing anemia ?</i>	Yes c No c àExclude Unclear c	
Types of outcome measures (anemia or hemoglobin levels): defined as Hb < 12.0 g/dl or Hct <36% among non-pregnant women, and Hb <11.0 g/dl or Hct <33.0% among pregnant women.	List outcomes:	Give definition of anemia used by author:	
	<i>Do the outcome measures meet the criteria for inclusion?</i>	Yes c No c àExclude Unclear c	
Year of Publication 2000 to 2020	<i>Is the identified article published between 2000 and 2020?</i>	Yes c No c àExclude Unclear c Specify the year---- ----	
Language of the published article English language	<i>Is the identified article published in English language?</i>	Yes c No c àExclude Unclear c Specify the language-----	
Type of journal Peer reviewed journal (<i>Check from the list of all relevant journals or run a google search</i>)	<i>Is the identified journal peer reviewed?</i>	Yes c No c àExclude Unclear c Specify the journal -----	

Summary of Assessment for Inclusion

Include in review c		Exclude from review c	
Independently assessed by two authors, and then compared? Yes c No c		Differences resolved Yes c No c	
Notes:			

Table 3: Search strategy according to PICO criteria	
Population	'women*' [Mesh] OR 'women*reproductive age*' OR pregnant* OR married* OR non-pregnant* OR 'married woman*' OR 'married pregnant woman' OR 'married non-pregnant woman' OR 'pregnant women' 'reproductive age' OR 'non-pregnant women' 'reproductive age' [Mesh]) AND
Intervention	Iron supplements OR Iron therapy OR Iron tablets [MeSH Terms]) OR Iron fish [MeSH Terms]) OR Iron fortification [MeSH Terms]) OR iron medication [MeSH Terms]) OR iron in any form [MeSH Terms]) OR iron syrup [MeSH Terms]) OR iron rich diet[MeSH Terms]) OR iron rich fruits, vegetables, meat [MeSH Terms]) AND
Comparison	Women without anemia or non-anemic women
Outcome	Anemia OR Hemoglobin levels OR Hemoglobin concentrations OR Hemoglobin status OR low Hemoglobin levels OR low Hemoglobin concentrations OR 'low hematocrit levels' OR Anemia symptoms OR paleness AND
Setting	Developing country OR developing nation OR least developed country OR least developed nation OR less developed nation OR third world country OR third world nation OR under developed country OR remote region OR low and middle income country OR under developed nation OR low and middle income nation OR developing countries in Africa OR developing countries in Asia OR Bangladesh OR Bhutan OR Indonesia OR Timor-Leste OR Kenya OR Ghana OR Kiribati OR Uzbekistan OR Kosovo OR Vanuatu OR Pakistan OR Vietnam OR India OR Democratic republic of Congo OR Ethiopia OR Zambia OR Uganda.

Figures

Figure 1

Flow chart summarizing the identification and selection of papers for systematic review