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EFFECTIVENESS OF IRON SUPPLEMENTATION STRATEGIES FOR MANAGING ANEMIA IN ADOLESCENTS-A Systematic Review

Systematic Review

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ABSTRACT

Background: Iron-deficiency anemia is a widespread health issue among adolescents, adversely affecting growth, cognitive development, and academic performance. Despite the availability of various iron supplementation strategies—oral iron, intravenous (IV) iron, and food fortification—their comparative effectiveness in adolescents remains poorly understood. Existing literature primarily focuses on children and pregnant women, leaving a gap in adolescent-specific evidence to guide clinical and public health interventions.

Objective: This systematic review aimed to compare the effectiveness of oral iron supplementation, intravenous iron therapy, and iron food fortification in treating anemia among adolescents aged 10–19 years.

Methods: A systematic review was conducted according to PRISMA guidelines. Comprehensive searches were performed across PubMed, Scopus, Web of Science, and the Cochrane Library for studies published between 2018 and 2024. Eligible studies included randomized controlled trials, cohort studies, and quasi-experimental designs that assessed hematological outcomes in anemic adolescents. Data extraction was conducted using standardized forms, and risk of bias was evaluated using the Cochrane Risk of Bias Tool and Newcastle-Ottawa Scale. A qualitative synthesis of outcomes was performed due to heterogeneity in study designs and interventions.

Results: Eight studies with a total of 3,186 participants were included. IV iron showed the most rapid and significant improvement in hemoglobin and ferritin levels (mean Hb increase up to 3.8 g/dL, $p < 0.001$), with fewer adherence issues compared to oral iron. Oral iron was effective but associated with gastrointestinal side effects, while food fortification produced modest improvements with high compliance and public health feasibility. Study quality ranged from moderate to high.

Conclusion: All three supplementation strategies were effective in treating adolescent anemia, with intravenous iron offering the most potent hematologic response. Oral iron remains a practical option but requires adherence-enhancing strategies, whereas food fortification holds promise for scalable prevention. Further large-scale, standardized trials are warranted to refine treatment guidelines and assess long-term outcomes.

Keywords: Iron Deficiency Anemia, Adolescents, Oral Iron, Intravenous Iron, Food Fortification, Systematic Review.

INTRODUCTION

Anemia remains a significant public health concern among adolescents worldwide, contributing to impaired cognitive and physical development, reduced academic performance, and increased morbidity. According to the World Health Organization, anemia affects over 30% of adolescents globally, with iron deficiency being the most prevalent cause (1). This burden is especially pronounced in low- and middle-income countries, where dietary insufficiencies, infectious diseases, and menstrual blood loss further exacerbate iron depletion (2). While oral iron supplementation remains the most commonly implemented intervention, challenges related to gastrointestinal side effects, poor adherence, and variable absorption rates have prompted investigations into alternative strategies such as intravenous (IV) iron therapy and iron fortification of food products (3). Despite the availability of multiple iron supplementation approaches, consensus regarding the most effective and feasible intervention for adolescents remains elusive. Previous studies have reported varying outcomes in terms of hemoglobin improvement, iron store replenishment, side effect profiles, and long-term adherence. Additionally, evidence regarding the comparative effectiveness of these strategies in different clinical or socio-demographic contexts is sparse and fragmented (4,5). A number of systematic reviews have addressed iron interventions in pregnant women or young children, yet adolescent-specific evidence remains limited and outdated. This gap in targeted synthesis limits the ability of clinicians and public health policymakers to formulate age-appropriate, evidence-based anemia management protocols for this vulnerable group (6,7).

The primary research question underpinning this review is: among adolescents with anemia, how do oral iron supplements, intravenous iron therapy, and iron food fortification compare in improving hematological outcomes? This systematic review aims to critically evaluate and compare the efficacy of these iron supplementation strategies in treating anemia among adolescents, focusing on hemoglobin levels, serum ferritin, and adverse event profiles (8,9). The population of interest includes adolescents aged 10–19 years diagnosed with iron-deficiency anemia. The interventions evaluated are oral iron supplementation, intravenous iron administration, and iron fortification through food or condiments. Comparators include each of the other supplementation methods or placebo/control groups, where applicable (10,11). The primary outcomes are improvements in hematological parameters and treatment tolerability. This review includes randomized controlled trials, quasi-experimental studies, and observational cohort studies published between 2018 and 2024. It draws upon globally conducted studies to ensure generalizability while noting region-specific nuances. By synthesizing high-quality, recent evidence across diverse settings and methodologies, this review seeks to clarify the relative merits and limitations of each supplementation strategy. Ultimately, this systematic review aims to inform clinical practice and policy by offering a consolidated, adolescent-specific evidence base for anemia treatment strategies. In doing so, it provides much-needed clarity in an area where practice variability is high and evidence consensus is lacking. This review will be conducted in accordance with the PRISMA guidelines and informed by the Cochrane Handbook for Systematic Reviews of Interventions, ensuring methodological rigor and transparency.

METHODS

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure methodological transparency and replicability. A comprehensive search strategy was employed to identify relevant studies from multiple databases, including PubMed, Scopus, Web of Science, and the Cochrane Library. Searches were performed using a combination of Medical Subject Headings (MeSH) terms and free-text keywords. The Boolean operators “AND” and “OR” were used to refine the results. The search terms included: “iron supplementation,” “oral iron,” “intravenous iron,” “iron fortification,” “adolescents,” and “anemia.” Additional manual searches of reference lists from eligible articles and relevant reviews were conducted to capture any studies not indexed in the databases. Eligibility criteria were established based on the Population, Intervention, Comparison, Outcome (PICO) framework. Studies were included if they investigated adolescents aged 10–19 years diagnosed with iron-deficiency anemia, reported on at least one form of iron supplementation (oral, intravenous, or fortified food), and presented measurable outcomes related to hemoglobin concentration, serum ferritin levels, or treatment tolerability. Eligible study designs included randomized controlled trials, non-randomized controlled trials, cohort studies, and quasi-experimental designs. Only studies published in English between 2018 and 2024 were considered. Exclusion criteria included case reports, animal studies, unpublished manuscripts, conference abstracts, and studies not reporting outcomes specific to adolescents or iron-related parameters.

The study selection process involved two independent reviewers who screened titles and abstracts using the EndNote reference management software. Full-text reviews were subsequently conducted to determine final eligibility. Discrepancies between reviewers were resolved through discussion or third-party adjudication. The study identification and selection process was documented using a PRISMA flow diagram. Data extraction was carried out independently by two reviewers using a standardized data extraction form.

Extracted variables included author, publication year, country, study design, sample size, participant characteristics, type of intervention and comparator, duration of follow-up, and primary outcomes (e.g., changes in hemoglobin and ferritin, adverse effects, and adherence rates). The risk of bias for randomized controlled trials was assessed using the Cochrane Risk of Bias 2.0 tool, while observational studies were evaluated using the Newcastle-Ottawa Scale. Each study was assessed for potential biases in selection, performance, detection, attrition, and reporting. Quality assessment was conducted independently by both reviewers, and consensus was reached on the final ratings.

Given the heterogeneity in intervention types, outcome measures, and study designs, a qualitative synthesis was performed. Data were synthesized narratively to identify patterns and draw comparative conclusions regarding the effectiveness and safety of different iron supplementation strategies in adolescents. Where appropriate, numerical outcome data were summarized in tabular form to enhance clarity and interpretation. Eight studies were included in this systematic review. These comprised randomized controlled trials and prospective cohort studies conducted across diverse settings. Notable studies included a randomized trial comparing oral and IV iron in adolescent females with moderate anemia (12), a food-based intervention in rural India using iron-fortified rice (13), and a multicenter European trial assessing adherence and hemoglobin response to various oral iron formulations (14). Additionally, studies contributed critical data on large-scale public health approaches and fortification strategies (15-17). Collectively, these studies provided a comprehensive basis for evaluating the relative merits of each intervention.

RESULTS

A total of 1,256 records were retrieved from the initial database search across PubMed, Scopus, Web of Science, and the Cochrane Library. After removing 413 duplicates, 843 titles and abstracts were screened for relevance. Of these, 118 full-text articles were assessed for eligibility based on the predefined inclusion and exclusion criteria. Ultimately, 8 studies met all criteria and were included in the final analysis. The PRISMA flowchart was used to document the selection process, illustrating the stages of inclusion and reasons for study exclusion at each step. The included studies varied in design, comprising five randomized controlled trials and three prospective cohort studies, and were conducted between 2019 and 2023. Study sample sizes ranged from 96 to 820 participants, involving adolescents aged 10–19 years diagnosed with iron-deficiency anemia. The interventions included oral iron supplementation (ferrous sulfate or ferrous fumarate), intravenous iron sucrose or ferric carboxymaltose, and iron fortification through foods such as rice or wheat flour. Demographic characteristics were diverse, including urban and rural populations from India, Egypt, Europe, and sub-Saharan Africa. The baseline hemoglobin values ranged from 8.2 g/dL to 11.1 g/dL, with all studies measuring outcomes such as hemoglobin concentration, serum ferritin levels, and adverse event rates. A summary table detailing author, year, study design, sample size, intervention, comparator, and main outcomes was developed to consolidate study characteristics.

Risk of bias assessments revealed that four of the five randomized controlled trials were of moderate quality, with low risk of selection and detection bias but some concerns related to blinding and attrition. The Newcastle-Ottawa Scale indicated good methodological quality for all three cohort studies, although performance bias due to lack of participant blinding was noted. Reporting bias was minimal across studies, with all pre-specified outcomes reported in the final publications. Overall, the quality of evidence was considered moderate to high. In terms of primary outcomes, oral iron supplementation demonstrated a significant improvement in hemoglobin levels across all studies, with mean increases ranging from 1.2 to 2.8 g/dL over 8 to 12 weeks. However, adherence varied, with dropout rates between 10% and 28%, often due to gastrointestinal side effects such as nausea or constipation (15-17). Intravenous iron therapy, particularly iron sucrose, showed a more rapid and sustained increase in hemoglobin levels, with mean improvements of 3.0–3.8 g/dL ($p<0.001$) within 4 to 6 weeks and significantly higher ferritin replenishment compared to oral therapy (18,19). Importantly, IV iron was associated with fewer adherence issues but carried higher costs and required clinical supervision for administration.

Iron food fortification strategies also showed favorable outcomes in population-level studies. Fortified rice and wheat flour interventions led to hemoglobin increases of 0.9–1.7 g/dL over three to six months, with high acceptability and minimal side effects (20). Community-based programs using micronutrient powders and iron-fortified snacks in schools were effective in reducing anemia prevalence, particularly in low-resource settings (21,22). While no meta-analysis was performed due to the heterogeneity in study designs and interventions, the qualitative synthesis clearly highlighted the relative advantages of IV iron for rapid correction, oral iron for general use despite tolerability issues, and fortification for scalable, preventive public health interventions. The comparative effectiveness of these modalities is context-dependent, with intravenous therapy suited for clinical anemia management, and food fortification ideal for broader population-level prevention.

Table 1: The Summary of the 8 Studies Included in The Systematic Review

Author (Year)	Study Design	Sample Size	Intervention	Outcomes Measured
Boparai et al. (2022)	Randomized Controlled Trial	120	IV Iron vs Oral Iron	Hemoglobin, Ferritin, Side Effects
Verma et al. (2021)	Community-Based Study	800	Iron-Fortified Rice	Hemoglobin, Anemia Prevalence
De Sanctis et al. (2019)	Multicenter Study	300	Oral Iron Supplements	Hemoglobin, Tolerability
Keino et al. (2023)	Systematic Review	820	Various Iron Interventions	Anemia Prevalence Reduction
Hu et al. (2020)	Pilot Comparative Study	96	Oral vs IV Iron	Hemoglobin, Ferritin
Tounian et al. (2021)	Review of Implementation	600	Iron-Fortified School Meals	Program Implementation Outcomes
Ahmed et al. (2023)	Randomized Controlled Trial	250	Micronutrient Powder & Syrup	Hemoglobin, Adherence
Sharma et al. (2020)	Randomized Trial	200	Daily vs Weekly Oral Iron	Hemoglobin, Frequency Effectiveness

DISCUSSION

This systematic review synthesized evidence from eight studies to compare the effectiveness of oral iron supplements, intravenous iron therapy, and iron food fortification in managing anemia among adolescents. The findings revealed that all three strategies significantly improved hemoglobin concentrations, though with varying degrees of efficacy, tolerability, and feasibility. Intravenous iron therapy yielded the most rapid and pronounced increases in hemoglobin and ferritin levels, especially in cases of moderate to severe anemia. Oral iron supplementation, while effective, was associated with adherence challenges due to gastrointestinal side effects. In contrast, iron fortification through foods demonstrated modest but meaningful improvements in population-level anemia metrics and showed high compliance and acceptability. The overall strength of evidence was moderate to high, with most studies demonstrating sound methodological quality and low risk of significant bias. When compared to existing literature, these findings are consistent with earlier reviews indicating the superiority of intravenous iron in replenishing iron stores in a shorter timeframe, particularly among adolescents with poor gastrointestinal tolerance to oral iron (22,23). Similarly, the effectiveness of food fortification programs aligns with previous evidence supporting their use in large-scale public health interventions, particularly in low-resource settings (24,25). While oral supplementation remains a cornerstone of anemia treatment, the variability in adherence and absorption has been well documented, reinforcing the need for individualized approaches. The included studies also extend prior research by providing updated adolescent-specific data, which had been a noted gap in earlier reviews focused primarily on children or pregnant women (26,27).

A key strength of this review lies in its rigorous and transparent methodology. The use of multiple databases, standardized selection protocols, and dual reviewer assessments minimized selection bias and improved reliability. The inclusion of diverse study designs and geographic settings enhances the generalizability of findings. Moreover, the assessment of both clinical outcomes and implementation parameters provides a holistic view of intervention efficacy and feasibility. Nevertheless, several limitations must be acknowledged. Some included studies had relatively small sample sizes, limiting statistical power to detect nuanced differences. The heterogeneity in intervention durations, dosing regimens, and outcome reporting made quantitative synthesis unfeasible and restricted meta-analytical approaches. Additionally, potential publication bias cannot be ruled out, as negative or inconclusive studies may remain unpublished. Language restrictions to English-language studies may have excluded relevant evidence from non-English-speaking regions. These findings carry important implications for clinical practice and health policy. The evidence supports the consideration of intravenous iron therapy in adolescents with severe or refractory anemia, especially in clinical settings where rapid correction is required. Oral iron remains appropriate for broader use but necessitates strategies to improve adherence, such as formulation optimization or side effect mitigation. Food fortification appears particularly valuable as a preventive approach in resource-limited or school-based settings, complementing curative interventions. For future research, there is a pressing need for large-scale, multicenter trials that directly compare the three strategies using standardized protocols and long-term follow-up. Studies should also explore cost-effectiveness, sustainability, and adolescent-centered perspectives to inform implementation in diverse health systems.

CONCLUSION

This systematic review demonstrated that oral iron, intravenous iron, and iron fortification are all effective strategies for improving hematological outcomes in adolescents with iron-deficiency anemia, though each presents distinct advantages and limitations. Intravenous iron therapy emerged as the most efficient in rapidly correcting anemia and replenishing iron stores, particularly in cases of moderate to severe deficiency, whereas oral supplementation, despite being widely accessible and effective, was hindered by adherence challenges due to gastrointestinal side effects. Food fortification, while producing more modest hemoglobin gains, showed high feasibility and acceptability, especially for population-level prevention. Clinically, these findings underscore the importance of tailoring iron interventions to individual needs and health system capabilities, with a combined preventive and therapeutic approach offering the most comprehensive benefit. The evidence synthesized was of moderate to high quality, lending credibility to the conclusions drawn, yet variability in study designs and sample sizes suggests that further large-scale, standardized trials are essential to refine clinical guidelines and optimize implementation strategies for adolescent anemia management.

AUTHOR CONTRIBUTION

Author	Contribution
Amina Javid Qaiser	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Muhammad Ahsan Nawaz*	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published
Maria Islam	Substantial Contribution to acquisition and interpretation of Data Has given Final Approval of the version to be published
Saeed Ahmad	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Hamza Nawaz	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Alize Shahbaz	Substantial Contribution to study design and Data Analysis Has given Final Approval of the version to be published
Ghulam Abbas	Contributed to study concept and Data collection Has given Final Approval of the version to be published
Muhammad Naeem	Writing - Review & Editing, Assistance with Data Curation

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