

TITLE: Oral Iron for Anemia: A Review of the Clinical Effectiveness, Cost-effectiveness and Guidelines

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CONTEXT AND POLICY ISSUES

Anemia is a condition in which circulating red blood cells (RBCs) are deficient with regards to quality and/or quantity.¹ A generally accepted working definition of anemia in the adult is a hemoglobin level less than the normal mean minus two standard deviations.² Iron deficiency is the most common cause of anemia. Iron deficiency anemia (IDA) is characterized by small RBCs (microcytic), which are relatively pale (hypochromic) in color relative to normal red cells. It develops in sequence to a reduction in iron stores manifesting as low serum ferritin usually with normal sized RBC in its early stages, and progressing to depleted iron stores when the ferritin level falls below 12 mcg/L.³ Based on data from the 2009 to 2011, a 2012 Statistics Canada report indicated that 4% of Canadians had low serum ferritin while 3% had low hemoglobin anemia.⁴ Iron deficiency anemia (IDA) is most prevalent among preschool children and women. Approximated 75% of all diagnosed cases of anemia in pregnancy is attributed to iron deficiency.⁵⁻⁷

Iron-deficiency anemia impacts negatively on the affected patients by disturbing the function of body systems such as the central nervous system (CNS), the immune, cardiorespiratory and vascular systems, as well as the genital and gastrointestinal tracts.⁸ The consequence of such disruptions may include impaired cognitive function, fatigue, depression, and alterations in cell functions. Iron-deficiency anemia may also result in breathing difficulties, palpitations, risk of cardiac failure, loss of libido, menstrual problems, anorexia, nausea, and motility disorders.⁸ Iron-deficiency anemia is associated with maternal mortality, prenatal and perinatal infant loss, premature births, and infants with less than one-half of normal iron reserves. It is estimated that IDA reduces favorable pregnancy outcomes by 30 to 45%.^{3,5}

Successful management of iron deficiency anemia requires identification and treatment of the underlying cause(s) of the iron deficiency.⁷ Treatment options for IDA include dietary measures and administration of iron supplements, with selection driven by the severity of the condition and the ability of the patient to tolerate the intervention.^{7,9} Patients with mild or moderate IDA are usually treated with oral iron supplements administered as elemental iron at a dose of 3 mg/kg

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per day, for an average duration of six to eight weeks. Parenteral iron therapy is reserved for patients with severe, persistent anemia who are unresponsive or have proven intolerance to oral supplements. It may also be given to patients with malabsorption or poor compliance to oral iron supplements.⁹

Oral iron salts such as ferrous fumarate, ferrous gluconate, and ferrous sulfate have been the mainstay of oral iron supplementation because they are inexpensive, effective at restoring iron balance, and have good overall safety and tolerability profile. However, in some patients, absorption of oral iron salts is inadequate, and poor tolerance results in reduced adherence to therapy. Polysaccharide iron complex and heme iron polypeptide products have become available as alternative therapies, offering improved absorption and tolerability profile over the traditional iron salts. However, they are significantly more expensive than iron salts. The aim of this review is to summarize current evidence on the comparative clinical and cost effectiveness of oral and injectable iron supplementation products for IDA.

RESEARCH QUESTIONS

1. What is the clinical effectiveness of oral iron complex products compared with oral iron salts for patients with anemia?
2. What is the clinical effectiveness of oral iron complex products compared with injectable iron supplements for patients with anemia?
3. What is the comparative clinical effectiveness of different oral iron complex products?
4. What is the cost-effectiveness of oral iron complex products for patients with anemia?
5. What are the evidence-based guidelines for the treatment of iron deficiency with oral iron products?

KEY FINDINGS

Among chronic kidney disease (CKD) patients with iron deficiency anemia (IDA), oral heme iron polypeptide (HIP) was comparably effective compared with intravenous (IV) iron preparations or oral ferrous sulfate to improve hemoglobin levels and transferrin saturation. However, both IV iron and oral ferrous sulfate improved serum ferritin levels to a significantly higher level than HIP in CKD patients with IDA. Oral ferrous sulfate is similarly effective to either oral iron polymaltose complex (IPC) or iron-zinc combination preparations to improve hemoglobin levels in children with IDA aged between 6 months and 15 years. Oral ferrous sulfate has comparable efficacy as oral IPC for the treatment of IDA during pregnancy. Although oral IPC was associated with a lower incidence of adverse events compared with ferrous sulfate for the treatment of IDA during pregnancy, both interventions were generally well tolerated with no serious adverse events occurring with either treatment. No studies which compared the clinical or cost effectiveness of different oral iron complex products for patients with anemia were identified.

METHODS

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, Canadian and major international health technology agencies, as well as a focused Internet search. Filters were applied to specific questions to limit the retrieval to health technology assessments, systematic reviews, randomized controlled trials, economic studies, and guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2010 and November 30, 2015.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Population	Patients with anemia
Intervention	Oral polysaccharide iron complex (e.g. Triferexx, Feramax, Jamp Ferrous polysaccharide, Niferex, Polyride-FE) or heme iron polypeptide (Proferrin, Jamp-Iron Polypeptide)
Comparator	Oral iron salt (e.g. ferrous sulfate, ferrous fumarate, ferrous gluconate) Oral iron complex products compared with each other Injectable iron supplements
Outcomes	Clinical effectiveness (e.g. improved anemia), safety and harms, cost-effectiveness, evidence-based guidelines
Study Designs	HTA/Systematic Reviews/Meta-Analyses, Randomized Controlled Trials, Economic Evaluations, Evidence-based Clinical Guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to January 1, 2010. Review articles not based upon a systematic literature search, studies which broadly described the intervention or comparator as oral iron without specifying the kind (salts or complexes), and primary studies included in a systematic review already selected to be included in this report were also excluded. Guidelines which targeted populations in specific geographical locations and thus present uncertainty about generalizability, and guidelines which were based on expert opinion without evidentiary support were excluded.

Critical Appraisal of Individual Studies

The included systematic review was critically appraised using AMSTAR¹⁰ while the randomized controlled trials (RCTs) were critically appraised using the Downs and Black checklist for measuring quality of studies,¹¹ and the guideline was assessed with the AGREE II instrument.¹² Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively. The strengths and limitations of the individual studies are summarized in Appendix 3.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 362 citations were identified in the literature search. Following screening of titles and abstracts, 340 citations were excluded and 22 potentially relevant reports from the electronic search were retrieved for full-text review. Five potentially relevant publications were retrieved from the grey literature search. Of the 27 potentially relevant papers, 23 publications were excluded for various reasons, while four publications met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Additional references of potential interest that did not meet the selection criteria are provided in Appendix 5.

Summary of Study Characteristics

A summary of individual study characteristics is provided in Appendix 2.

Study Design

One systematic review,¹³ two randomized controlled trials (RCTs),^{5,14} and one clinical guideline¹⁵ met the inclusion criteria of this review. The systematic review was published in 2015 and included three primary active-control studies published between 2003 and 2013. One of the primary studies was had a single-blind design while two were open-label RCTs. One of the selected RCTs¹⁴ for this review was a single-setting study published in 2015 and the other was a multicenter RCT⁵ published in 2011. Both RCTs^{5,14} had an open-label design. The clinical guideline was published in 2013.

Country of Origin

The systematic review¹³ was performed by authors from the United States of America (USA) with primary studies conducted in Australia, Canada, and the USA. One of the RCTs was conducted in Turkey,¹⁴ while the other was conducted at multiple centers in Argentina and Colombia.⁵ The clinical guideline¹⁵ was produced by the American College of Obstetricians and Gynecologists (ACOG) in the USA.

Patient Population

The systematic review involved 161 chronic kidney disease (CKP) patients with iron deficiency anemia, made up of 40 participants from one primary RCT who were not using dialysis, 59 patients on hemodialysis from another primary study, and 62 patients from a third primary study

who used peritoneal dialysis. Among patients who were not on any dialysis, baseline hemoglobin and ferritin levels ranged from 108.5 g/dL to 110.5 g/dL and 67 µg/L to 71 µg/L, respectively, while transferrin saturation was 17% for all treatment groups. The systematic review did not report similar iron indices for its two other primary studies.

One of the selected RCTs¹⁴ for this review included 60 children with iron deficiency anemia ranging in age from 6 months to fifteen years old. At baseline, the treatment groups had mean hemoglobin levels between 8.6 ± 1.0 g/dL and 9.6 ± 0.5 g/dL, and mean corpuscular volume (MCV) between 60.2 ± 7.5 fL and 63.9 ± 6.6 fL. Transferrin saturation (TSAT) was between 4.0% and 5.0% while serum ferritin levels were between 8.8 ng/mL and 20.0 ng/mL. The other RCT⁵ included 80 pregnant women (16 years or older) with gestational age between 18 and 26 weeks who had been diagnosed with iron deficiency anemia. At baseline, they had hemoglobin level ≤ 10.5 g/dL, mean corpuscular volume (MCV) < 80 fL, and serum ferritin level ≤ 15 ng/mL.

The targeted patient group of the clinical guideline was pregnant women with IDA.

Interventions and Comparators

For the systematic review,¹³ one of the primary studies compared oral HIP complex (11 mg three times daily) with IV iron sucrose (200mg monthly) for 6 months. Another primary study compared two different doses of oral HIP (21 mg daily and 36 mg daily) with IV iron (administered per site protocol), while the third primary study compared oral HIP (12 mg twice daily) with oral ferrous sulfate (105 mg elemental iron twice daily). The duration of treatment was 6 months for each of the primary studies. All the patients in the three primary studies of the systematic review were on concomitant treatment with erythropoiesis stimulating agents (ESA) while being treated with the study drugs.

One selected RCT¹⁴ for this review randomized patients to one of ferrous sulfate, IPC, or iron-zinc combination product (elemental iron to zinc ratio 40:15 mg), all administered orally for eight weeks. A therapeutic dose of 6 mg/kg daily for eight weeks was set for iron, followed by a maintenance dose of 2 mg/kg daily for the next eight weeks. However, results for the eight weeks treatment phase was the focus of the study. Another included RCT⁵ assigned patients to oral treatment with 100 mg iron twice daily for 90 days using IPC or ferrous sulfate.

The IDA interventions in the clinical guidelines referred to oral and IV iron supplementation as well as pack cells or blood transfusion. To answer the specific questions of this review, pack cells or blood transfusion have not been included subsequent discussions.

Outcomes

Change from baseline in hemoglobin levels was the most common efficacy outcome measure of interest, reported by the systematic review¹³ and the two RCTs.^{5,14} Serum ferritin levels and TSAT were outcome measures in the systematic review,¹³ and one RCT⁵ which also reported on serum iron levels and hematocrit. The systematic review¹³ also reported on changes in ESA dosing and sensitivity index following iron supplementation therapy. The ESA sensitivity index was derived by dividing the total weekly dose by the hemoglobin level.

Summary of Critical Appraisal

The systematic review¹³ was based on studies selected from a systematic search of electronic databases, supplemented by an evaluation of the bibliography of the relevant articles for additional studies. Three primary studies were included in the systematic review,¹³ and the criteria for study selection and data extraction were not described. Moreover, one of the three primary studies was not fully randomized because patients from a study site who were supposed to receive intravenous iron were given supplementation with HIP because they did not have a reimbursement plan for the intravenous product. Furthermore, the studies were not assessed for methodological quality or publication bias, and a list of excluded studies was not provided. Therefore, the systematic review is limited by the small number of primary studies, a high potential for selection bias, and inability to assess the robustness of its findings since its primary studies were not graded for quality. In addition, information about patient characteristics and the settings of the included studies was not well reported, making it difficult to assess the generalizability of the study findings to Canadian settings and context. The authors declared no conflict of interest and they received no funding for the study.¹³

The two RCTs^{5,14} described their study objectives, interventions of interest, and main outcomes to be measured clearly. In addition, both studies^{5,14} defined their inclusion and exclusion criteria, and provided relevant patient characteristics. In each study,^{5,14} participants were randomly assigned to their respective treatments, and baseline characteristics were similar across treatment groups. Both RCTs^{5,14} had small sample sizes, and since none of them performed a sample size and power calculation, it is uncertain whether any of them was sufficiently powered to detect relevant differences in outcomes between treatment groups. One RCT¹⁴ had a high drop-out rate (25%). The distribution of drop-outs across the treatment groups was not reported and there was no information about how missing data was treated. In the other RCT,⁵ a total of four (0.5%) participants discontinued prematurely, two from each treatment group. Missing data was treated using the last observation carried forward (LOCF) approach. One RCT¹⁴ provided no information about blinding or concealment of treatment assignment, while the other RCT⁵ was an exploratory, open-label study. However, this design and reporting limitations are unlikely to influence the reported efficacy outcomes since they were objectively determined. However, adverse events outcomes are susceptible to bias in open-label studies. The generalizability of the findings of the two RCTs^{5,16} to Canadian settings is unknown since both were conducted in foreign countries, with little or no information about the settings of the study. Researchers in one of the RCTs⁵ received funding and travel grants from a pharmaceutical company which also funded the study. It is unknown whether this apparent conflict of interest biased the study and the reporting of its findings. Authors of the other RCT¹⁴ declared no conflict of interest, and received no funding for the study.

The guideline¹⁵ had well-described objectives, targeted professional users, and population to whom it was meant to apply. Evidence was collected through systematic manual and electronic searches of relevant databases. The quality and strength of evidence was reported using a clearly described rating scheme. The recommendations were based on expert consensus, with the strength of each recommendation appropriately linked to the supporting evidence. Drafts of the guideline were validated by two internal clinical review panels composed of practicing obstetrician-gynecologists, generalists and sub-specialists, while the final guidelines were reviewed and approved by the American College of Obstetricians and Gynecologists (ACOG) Executive Board.

However, some quality measures such as the criteria for selection of evidence and the procedure for updating the guideline,¹⁵ which are determinants of rigor of development, were not available for assessment. Moreover, the guideline did not provide advice on how the iron supplementation should be executed. The place in therapy of the various formulations (oral and parenteral) for iron supplementation to treat IDA was not discussed. In addition, there was no information about the comparative effectiveness of the traditional interventions and the newer oral iron complexes and iron polypeptide products, and issues about facilitators or barriers to their application were not discussed. These limitations must be interpreted with consideration to the fact that only a summary form of the guideline was available for this review and a full version could not be retrieved. Thus, whether the full-version document responds adequately to these limitations is unknown.

Summary of Findings

The following is a summary of findings from one systematic reviews¹³ two RCTs^{5,14} and a clinical guideline¹⁵ included in this review. Appendix 4 provides further details of findings of the individual studies.

What is the clinical effectiveness and of oral iron complex products compared with oral iron salts for patients with anemia?

One systematic review¹³ compared the clinical efficacy of oral heme iron polypeptide (HIP) with oral ferrous sulfate in patients with chronic kidney disease with iron deficiency anemia (IDA) and reported that the treatments had comparable efficacies with regards to improvement from baseline in hemoglobin levels and transferrin saturation, as well as the mean dosage and sensitivity index of darbepoetin, an erythropoiesis stimulating agent (ESA). However, improvements in serum ferritin levels were significantly higher ($P = 0.01$) with oral ferrous sulfate compared with oral HIP (292mcg/L versus 124 mcg/L; $P = 0.003$, respectively). The incidence of adverse events was similar for both interventions.

One RCT¹⁶ comparing the efficacy of oral forms of ferrous sulfate, iron polymaltose complex (IPC) and an iron-zinc combination product for IDA in children found that the three treatments had comparable effectiveness to improve hemoglobin levels after 8 weeks of treatment. Another RCT⁵ found that after six months of treatment, oral IPC had, at least, a comparable efficacy as ferrous sulfate for the treatment of IDA in pregnant women. While there were no significant differences in the increase from baseline in hemoglobin levels and transferrin saturation at 90 days between the two interventions, the increases in hematocrit and serum ferritin levels were significantly higher among patients treated with oral IPC compared with those treated with ferrous sulfate ($6.62 \pm 2.04\%$ versus $5.81 \pm 2.4\%$, $P = 0.07$; and 64 ± 40 ng/mL versus 41 ± 28 ng/mL, $P = 0.004$, respectively). Although adverse events occurred significantly more frequently in the ferrous sulfate group, no serious adverse events occurred in either treatment group. The most commonly reported adverse events were nausea, vomiting and constipation.⁵

What is the clinical effectiveness of oral iron complex products compared with injectable iron supplements for patients with anemia?

One systematic review¹³ compared the effectiveness of oral HIP with that of IV iron to treat IDA in chronic kidney disease patients and reported that the treatments had comparable efficacies to improve hemoglobin levels and transferrin saturation from baseline. However, after six months of treatment, mean serum ferritin levels increased from 676 mcg/L at baseline to 723 mcg/L among patients treated with IV iron, while the mean serum ferritin levels decreased from 552 mcg/L at baseline to 446 mcg/L among patients treated with oral HIP. The difference was statistically significant ($P = 0.01$). Comparisons of the effect of HIP versus IV iron on ESA dosage in the participants produced inconclusive results. The reported incidence of adverse events was similar for the two interventions.

What is the comparative clinical effectiveness of different oral iron complex products?

The literature search for this review did not find any studies which compared the clinical effectiveness of different oral iron complex products for patients with anemia

What is the cost-effectiveness of oral iron complex products for patients with anemia?

The literature search for this review did not find any studies which compared the cost-effectiveness of oral iron complex products for patients with anemia

What are the evidence-based guidelines for the treatment of iron deficiency with oral iron products?

The literature search found one summary guideline¹⁵ for the treatment of IDA in pregnancy. While the document recommended iron supplementation for IDA in pregnancy (Grade C recommendation, based on consensus and expert opinion), it did not provide details of which formulations (oral or IV) should be used for IDA at different stages of pregnancy.

Limitations

The systematic review¹³ reported outcomes on an individual primary study basis without pooling results. Thus the benefit of effect estimate derived from appropriate combination of findings from multiple studies was not available from this systematic review.¹³ Furthermore, the quality of the primary studies included in the systematic was not assessed and there is reason to suspect that each of them had some undesirable quality issues. For example, there was no indication that any of primary studies was powered to detect relevant differences between treatment groups. Moreover, one of the three primary studies was not fully randomized because patients from a study site who were supposed to receive intravenous iron were given supplementation with HIP because they did not have a reimbursement plan for the intravenous product, and oral HIP was compared with suboptimal intravenous iron dose in another primary study. Furthermore, the study population of one primary study included iron-replete patients who do not fit the population of interest (patients with IDA) for this review.

The two RCTs^{5,14} selected for this review have limitations of small sample sizes and uncertainty about adequate power to detect relevant differences between treatment groups. In addition,

both were conducted in foreign countries and their findings may not be generalizable to Canadian settings.

The guideline¹⁵ lacks details about comparative advantages of the various iron supplementation interventions, and it is narrow in scope, targeting only pregnant women.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

One systematic review¹³ comprising three RCTs of uncertain quality found that among chronic kidney disease (CKD) patients with iron deficiency anemia (IDA), treatment with oral heme iron polypeptide (HIP) improved hemoglobin level and transferrin saturation to a similar level as treatment with oral ferrous sulfate or intravenous iron. Furthermore, both oral ferrous sulfate and intravenous iron improved serum ferritin to a significantly higher level than oral HIP in CKD patients with IDA. A randomized controlled study¹⁶ found that the effectiveness of oral iron polymaltose complex (IPC) to treat IDA in children was not significantly different from that of oral ferrous sulfate or oral iron-zinc combination preparation. Another RCT⁵ reported that the effectiveness of oral IPC to IDA during pregnancy was comparable to that of oral ferrous sulfate, although the frequency of adverse events was lower with IPC than with ferrous sulfate. The most commonly reported adverse events were nausea, vomiting and constipation, none of which was graded as severe.⁵

Overall, oral HIP and oral IPC preparations did not appear to confer superior efficacy benefit over traditional oral iron salt or intravenous iron supplementation for the treatment of iron deficiency anemia. Although one RCT⁵ reported that oral IPC had a superior safety profile compared to ferrous sulfate for the treatment of iron-deficiency anemia during pregnancy, both interventions were well tolerated by the patients, with no serious adverse events occurring in either treatment group.

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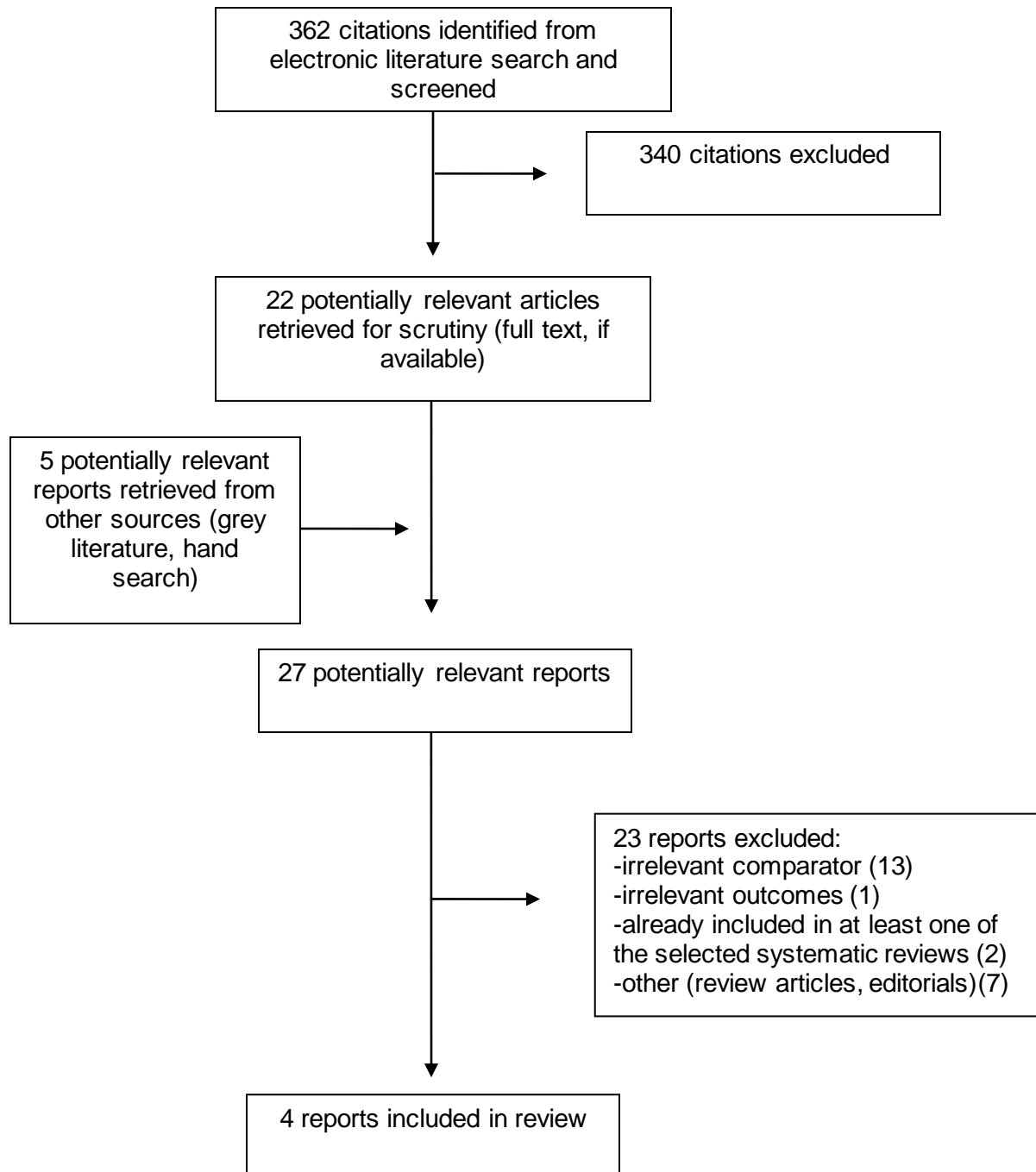
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APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Publications

Table A1: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Types and numbers of primary studies included	Population Characteristics	Intervention	Comparator(s)	Clinical Outcomes, Length of Follow-Up
Dull, 2015 ¹³ USA	Three RCTs	Patients (n=161) at various stages of CKD with anemia.	Oral HIP Intravenous iron sucrose,	Oral ferrous sulfate	Change from baseline in hemoglobin levels, hematocrit, and use of ESA (rHuEPO). Adverse events were also reported.
			Duration of follow-up was 6 months		

CKD = chronic kidney disease; ESA = erythropoiesis stimulating agent; HIP = heme iron polypeptide; RCTs = randomized controlled trials; rHuEPO = recombinant human erythropoietin

Table A2: Characteristics of Included Clinical Studies

First Author, Publication Year, Country, Study Name	Study Design	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes
Ozsurekci, 2015 ¹⁴ Turkey	Single-blind RCT	Children (n=60) with IDA, aged between 6 months and 15 years.	Oral Ferrous sulfate,	Oral IPC or a combined iron and zinc preparation.	Change from baseline in hemoglobin levels at weeks 1, 4 and 8.
			Eight weeks treatment		
Ortiz, 2011 ⁵ Argentina and Colombia	Multicenter, open-label RCT	Pregnant women (n=80, ≥16 years old, with gestation age between 18 and 26 weeks) diagnosed with IDA (hemoglobin ≤ 10.5 g/dL, serum ferritin ≤ 15 ng/mL and MCV < 80 fL).	Oral IPC	Oral ferrous sulfate	<p><u>Primary</u> Change from baseline in hemoglobin at days 60 and 90.</p> <p><u>Secondary</u> Mean serum ferritin at day 90, and adverse events</p>
			Each 100 mg iron twice daily for 90 days		

IDA = iron deficiency anemia; IPC = iron polymaltose complexes; MCV = mean corpuscular volume; RCT = randomized controlled trial

Table A3: Characteristics of Included Guidelines

Objectives			Methodology			
Intended users/ Target population	Intervention and Practice Considered ^a	Major Outcomes Considered ^a	Evidence collection, Selection and Synthesis	Evidence Quality and Strength	Recommendations development and Evaluation	Guideline Validation
American College of Obstetricians and Gynecologists, 2013 ¹³						
Physicians/ Pregnant women	<p>Iron supplementation</p> <ul style="list-style-type: none"> To aid practitioners in making decisions about appropriate obstetric and gynecologic care To provide a brief overview of the causes of anemia in pregnancy and review iron requirements To provide recommendations for screening and clinical management of anemia during pregnancy 	<ul style="list-style-type: none"> Effectiveness of screening for anemia during pregnancy Effectiveness of anemia prophylaxis during pregnancy 	<ul style="list-style-type: none"> Hand-searches of Published Literature (Primary Sources); Hand-searches of Published Literature (Secondary Sources); Searches of Electronic Databases 	<p>Each recommendation was supported by evidence graded as follows:</p> <p>I: Evidence obtained from at least one properly designed randomized controlled trial.</p> <p>II-1: Evidence obtained from well-designed controlled trials without randomization.</p> <p>II-2: Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.</p> <p>II-3: Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.</p> <p>III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.</p>	<p>Recommendations were ranked on the basis of supporting evidence as follows:</p> <p>Level A Based on good and consistent scientific evidence.</p> <p>Level B Based on limited or inconsistent scientific evidence.</p> <p>Level C Based primarily on consensus and expert opinion.</p>	Internal Peer Review

I.V. = intravenous; NR = not reported; WHO = World Health Organization

^a To answer the specific guidelines question for this review, discussion has been limited to oral iron interventions for the treatment of iron deficiency, including IDA.

APPENDIX 3: Critical Appraisal of Included Publications

Table A4: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR¹⁰

Strengths	Limitations
Dull, 2015 ¹³	
<ul style="list-style-type: none"> The primary studies were all RCTs selected from a comprehensive systematic literature search, including an evaluation of the bibliography of each relevant article for additional studies. The authors declared no conflict of interest and they received no funding for the article. 	<ul style="list-style-type: none"> Only three primary RCTs were included in the systematic review, and the results of these studies were not pooled to provide an effect estimate. None of the studies were double-blinded. While this may not affect the object efficacy outcome measures, the likelihood of type 2 error and bias with respect to adverse events cannot be ruled out. Sample size and power calculations were not reported in two of the primary studies, and the one primary study that reported such calculation had only a 56% power, Another primary study compared oral HIP with suboptimal intravenous iron dose, and included iron-replete HD-CKD patients who do not fit the population of interest for this review, In two of the primary studies, the analysis was based on the per-protocol not the ITT population. Thus it is unknown whether the reported outcomes reflect a truly randomized population. One of the primary studies had a 66% protocol deviation rate due to non-compliance, dose reductions or WDAEs. Thus the reported findings were based on only 46% of the total study population.

HD-CKD = hemodialysis chronic kidney disease, HIP = heme iron polypeptide; ITT = intention to treat; RCT = randomized controlled trial; WDAEs = withdrawal due to adverse events.

Table A5: Strengths and Limitations of Randomized Controlled Trials using Downs and Black¹¹

Strengths	Limitations
Ozsurekci, 2015 ¹⁴	
<ul style="list-style-type: none"> • A randomized controlled study with clearly described method of randomization of participant into treatment groups. • At baseline, hemoglobin levels and other hematological parameters (serum iron, TIBC, and ferritin levels) were not different between study groups. • Inclusion and exclusion criteria were clearly defined. • Outcome measures of interest were well-defined and methods of evaluation were described. • The authors had no conflict of interest, and there was no funding for the study. 	<ul style="list-style-type: none"> • The sample size was small and power determination was not done. Therefore, it is unknown if the study was sufficiently powered to detect relevant differences in outcomes between treatment groups. • Twenty-five percent (15 of 60) of the randomized patients were reported lost to follow-up. Details about how missing data were treated and the impact of missing data on the intervention groups were not provided. The high drop-out rate and the lack of details concerning distribution across study groups are potential sources of bias. • This was a single-center study performed in a teaching hospital outside Canada. Therefore, the findings may not be generalizable in health care provision settings in Canada.
Ortiz, 2011 ⁵	
<ul style="list-style-type: none"> • A randomized controlled study with clearly described inclusion and exclusion criteria. • Outcome measures of interest were well-defined and methods of evaluation of outcomes were described. • The relevant patients' characteristics including age, weight, gestational age, hemoglobin levels and RBC indices such as MCH, MCHC, and MCV were similar at baseline across treatment groups. • Analysis of efficacy outcomes was based on ITT population, and the discontinuation rate was low and identical across treatment groups, with missing data handled by the LOCF approach. Thus, the randomization effect at baseline was maintained. 	<ul style="list-style-type: none"> • Although it was an RCT, the study had an exploratory, open-label design. However the open-label design is unlikely to affect the objectively assessed efficacy outcomes, although AEs outcomes may be subject to bias. • No sample size calculation was performed; therefore it is uncertain whether the study was powered to detect relevant difference between treatment groups. • Some of the researcher received funding and travel grants from a pharmaceutical company which also funded the study. It is unknown whether this apparent conflict of interest biased the study and the reporting of its findings.

AEs = adverse events; IPC = iron polymaltose complexes; ITT = intention to treat population; LOCF = last observation carried forward; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; RBC = red blood cells; RCT = randomized controlled trial; TIBC = total iron binding capacity

Table A6: Strengths and Limitations of Guidelines using AGREE II¹⁴

Strengths	Limitations
<p>ACOG, 2013¹⁵</p> <ul style="list-style-type: none"> • The objectives, targeted users and population to whom it was meant to apply were well-described. • Relevant databases were systematically searched electronically and manually to collect evidence. • The quality and strength of evidence were reported using a clearly described rating scheme. • The recommendations were reached by consensus among experts. • The strength of each recommendation was linked to supporting evidence. • The guidelines were validated internally by clinical review panels composed of experts, as well as by the ACOG Executive Board who also approved the final document. 	<ul style="list-style-type: none"> • The guideline available for this review was in summary form. Therefore, it is unlikely that all important information was available for assessment. • There were no reviews by external experts. However, considering the specialized nature of the target population to whom the guidelines apply, it is unlikely that superior reviews could have been done outside the ACOG. • Some quality measures such as criteria for selection of evidence, procedure for updating the guideline, which are determinants of the rigor of processes and procedures for the development of the guideline, were not available for assessment. • There was no advice on how the iron supplementation should be implemented. • The guideline did not specify the place in therapy for the different formulations (oral or IV) of iron supplementation interventions, and there was no discussion of the newer oral iron complexes and polypeptides products.

ACOG = American College of Obstetrics and Gynecologists; IV = intravenous

APPENDIX 4: Main Study Findings and Author’s Conclusions

Table A7: Summary of Findings of Included Studies

Main Study Findings	Author’s Conclusions
Dull, 2015 ¹³	
<p><i>Hemoglobin levels</i></p> <ul style="list-style-type: none"> • One primary RCT of the systematic review¹³ found that at the end of 6 months treatment, oral HIP increased the median hemoglobin level from baseline to a similar extent as IV iron sucrose (117 g/dL versus 113 g/dL, respectively, $P = 0.37$) • Another primary RCT found that after 6 months treatment there was no significant difference in the median hemoglobin levels of patients who received oral HIP compared with those who received oral ferrous sulfate (111 g/dL versus 113 g/dL, respectively; $P = 0.59$). • One primary study found that overall, the change from baseline in hematocrit was similar in patients treated with oral HIP as those treated with IV iron, with both intervention showing no significant differences in the hematocrit levels from baseline after 6 months treatment (HIP = 34.8%, at baseline and 35.4% at 6 month; IV iron = 35.6% at baseline and 35.6% at 6 month). <p><i>Serum Ferritin levels</i></p> <ul style="list-style-type: none"> • One primary RCT of the systematic review¹³ reported that after 6 months treatment, the rise in the median ferritin levels was significantly higher in patients treated with IV iron compared with oral HIP (85.5, versus 244, $P = 0.004$; respectively) • One RCT found that 6 months treatment with IV iron resulted in an increase from baseline in the mean ferritin level (from 676 mcg/L to 723 mcg/L) while treatment with oral HIP resulted in a significant decrease from baseline in the mean ferritin level (from 552 mcg/L to 446 mcg/L; $P < 0.01$) • One RCT reported that median ferritin after 6 months of treatment was significantly higher among patients treated with oral ferrous sulfate compared with those treated with oral HIP (292 mcg/L versus 124 mcg/L; $P = 0.003$, respectively). <p><i>Transferrin saturation</i></p> <ul style="list-style-type: none"> • One primary RCT of the systematic review¹³ found no significant difference in TSAT between patients treated with oral HIP and those treated with IV iron after 6 months treatment (21.5% versus 21.5%; $P = 0.82$, respectively). A similar result was reported by another primary RCT of the systematic review 	<ul style="list-style-type: none"> • “Early clinical data in healthy volunteers suggest the bioavailability and tolerability of oral HIP is superior to non-heme iron supplementation, but these findings did not translate into improved iron indices in studies of patients with CKD. HIP is more expensive than oral non-heme iron. Overall, HIP does not appear to confer benefit over traditional iron supplementation among patients with anemia of CKD.”¹³ page 389

Table A7: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusions
<p>comparing oral HIP and oral ferrous sulfate (22% versus 20%; $P = 0.65$ respectively).</p> <p><i>Dosage and sensitivity of ESA</i></p> <ul style="list-style-type: none"> • One primary RCT of the systematic review¹³ found no significant difference in the mean rHuEPO dosage between patients treated with oral HIP and those treated with IV iron (60 mcg/month versus 50 mcg/month; $P = 0.56$, respectively) • Another RCT reported a significant decrease at 6 months in rHuEPO dosage from baseline (from 58,613 units/month, to 48,130 units/month; $P = 0.08$), while treatment with IV iron resulted in an increase in rHuEPO dosage at 6 months (from 32,996 units/month, to 35,127 units/month; $P = \text{NR}$). • One RCT found that after 6 months treatment the mean dosage and sensitivity index of DPO were similar among patients treated with oral HIP as among those treated with oral ferrous sulfate, with no significant difference between the interventions. <p><i>Adverse events</i></p> <ul style="list-style-type: none"> • Incidences of reported AEs were similar between oral HIP and IV iron, and between oral HIP and oral ferrous sulfate. The specifics of the AEs were not described. 	
<p>Ozsurekci, 2015¹⁴</p> <ul style="list-style-type: none"> • After eight weeks of treatment, there was no statistically significant difference in the impact on hemoglobin levels in children treated with oral IPC, ferrous sulfate, or iron-zinc combination product ($P > 0.05$). • For each of the three intervention groups, a significantly higher levels of hemoglobin were observed in patients after four weeks ($P = 0.001$) and eight weeks ($P < 0.001$) treatment compared to baseline. • No AEs were reported in any of the treatment groups. 	<ul style="list-style-type: none"> • After comparable effectiveness of ferrous sulfate, IPC, and iron-zinc combination preparation to treat IDA in children with IDA without AEs in any of the treatment groups, the investigators concluded that oral preparations of IPC or combination iron-zinc may be alternative choices to ferrous sulfate for the treatment of IDA in children.
<p>Ortiz, 2011⁵</p> <p><i>Hemoglobin levels and hematocrit</i></p> <ul style="list-style-type: none"> • After 90 days treatment, the mean hemoglobin level increased among patients who were treated with either oral HIP or oral ferrous sulfate. Changes from baseline to EOS were 9.64 ± 0.89 g/dL to 11.89 ± 0.53 g/dL in the oral IPC group compared with 9.79 ± 0.64 g/dL to 11.70 ± 0.76 g/dL in the ferrous sulfate group. There was no statistically significant difference between the treatment groups. 	<ul style="list-style-type: none"> • "Oral iron(III) polymaltose complex offers at least equivalent efficacy and a superior safety profile compared to ferrous sulfate for the treatment of iron-deficiency anemia during pregnancy."⁵ page 1347

Table A7: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusions
<ul style="list-style-type: none"> The increase from baseline in hematocrit was greater in the IPC group than the ferrous sulfate group. Changes from baseline to EOS were 29.08 ± 2.36 % to 35.83 ± 2.05 % for oral HIP and 29.26 ± 2.29 % to 35.03 ± 2.38 % for the ferrous sulfate group. The difference between the two groups was statistically significant ($P = 0.07$) <p><i>Serum Ferritin and Iron levels</i></p> <ul style="list-style-type: none"> After 90 days treatment, the increase in serum ferritin level from baseline was significantly higher in the IPC group than in the ferrous sulfate group. Changes from baseline to EOS were 113 ± 26 ng/mL to 179 ± 38 ng/mL in the IPC group, compared with 112 ± 29 ng/mL to 157 ± 34 ng/mL in the ferrous sulfate group, ($P = 0.004$). The increase in serum iron level from baseline was significantly higher in the IPC group than in the ferrous sulfate group after 90 days treatment. Changes from baseline to EOS were 5.8 ± 1.3 μmol/L to 11.4 ± 3.5 μmol/L in the IPC group compared with 5.7 ± 2.0 to 9.8 ± 2.9 in the ferrous sulfate group, ($P = 0.10$). <p><i>Transferrin saturation</i></p> <ul style="list-style-type: none"> Although the increase from baseline in TSAT was higher in the IPC group than in the ferrous sulfate group, the difference between the two groups was not statistically significant ($P = 0.21$) <p><i>Adverse events and Compliance</i></p> <ul style="list-style-type: none"> The most commonly reported adverse events were nausea, vomiting and constipation. Adverse events were significantly less frequent in the IPC group than in the ferrous sulfate group (29.3% versus 56.4%, respectively; $P = 0.015$). Non-compliance rate was significantly lower in the IPC group than the ferrous sulfate group, with significantly lower mean number of tablets returned from the IPC group than from the ferrous sulfate group (1.53 versus 2.97, respectively, $P = 0.015$) 	

AEs = adverse events; CKD = chronic kidney disease; DPO = darbepoetin; EOS = end-of-study; ESA = erythropoiesis stimulating agents; HIP = heme iron polypeptide; IDA = iron deficiency anemia; IPC = iron polymaltose complex; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; ND-CKD = non-dialysis dependent chronic kidney disease; PD = peritoneal dialysis; RCT = randomized controlled trial; rHuEPO = recombinant human erythropoietin; SD = standard deviation; TIBC = total iron binding capacity; TSAT = transferrin saturation

APPENDIX 5: Additional References of Potential Interest

Randomized controlled trials in included systematic reviews

- Nagaraju SP, Cohn A, Akbari A, Davis JL, Zimmerman DL. Heme iron polypeptide for the treatment of iron deficiency anemia in non-dialysis chronic kidney disease patients: a randomized controlled trial. *BMC Nephrol.* 2013;14:64. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3606612>.¹⁷
- Barraclough KA, Brown F, Hawley CM, Leary D, Noble E, Campbell SB, et al. A randomized controlled trial of oral heme iron polypeptide versus oral iron supplementation for the treatment of anaemia in peritoneal dialysis patients: HEMATOCRIT trial. *Nephrol Dial Transplant.* 2012 Nov;27(11):4146-53.¹⁸

Excluded for non-specific description of oral iron

- Wong G, Howard K, Hodson E, Irving M, Craig JC. An economic evaluation of intravenous versus oral iron supplementation in people on haemodialysis. *Nephrol Dial Transplant.* 2013 Feb;28(2):413-20.¹⁹

Excluded because they are expert opinions, lack evidentiary support, and/or have generalizability issues due to the targeted population

- Jayasekara R. Iron Deficiency Anemia: Treatment, The Joanna Briggs Institute, 2015²⁰
- Breyman C, Bian XM, Blanco-Capito LR, Chong C, Mahmud G, Rehman R. Expert recommendations for the diagnosis and treatment of iron-deficiency anemia during pregnancy and the postpartum period in the Asia-Pacific region. *J Perinat Med.* 2011 Mar;39(2):113-21.³
- Iron deficiency: investigation and management [Internet]. Vancouver (BC): British Columbia, Ministry of Health Services (Guidelines & Protocols Advisory Committee); 2010 [cited 2015 Dec 23]. http://www2.gov.bc.ca/assets/gov/health/practitioner-pro/bc-guidelines/iron_deficiency.pdf.²¹