OBSTETRICS & GYNECOLOGY

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- Comments from the reviewers and editors (email to author requesting revisions)
- Response from the author (cover letter submitted with revised manuscript)*

**The corresponding author has opted to make this information publicly available.*

Personal or nonessential information may be redacted at the editor's discretion.

Questions about these materials may be directed to the *Obstetrics & Gynecology* editorial office: obgyn@greenjournal.org.

Date: Jul 09, 2021
To: "Andra H. James" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-21-1259

RE: Manuscript Number ONG-21-1259

Iron deficiency anemia in pregnancy

Dear Dr. James:

Your manuscript has been reviewed by the Editorial Board and by special expert referees and it has been deemed for a revised version. We would also like this back within a week to meet publishing deadlines.

If you wish to consider revising your manuscript, you will first need to study carefully the enclosed reports submitted by the referees and editors. Each point raised requires a response, by either revising your manuscript or making a clear and convincing argument as to why no revision is needed. To facilitate our review, we prefer that the cover letter include the comments made by the reviewers and the editor followed by your response. The revised manuscript should indicate the position of all changes made. We suggest that you use the "track changes" feature in your word processing software to do so (rather than strikethrough or underline formatting).

Please be sure to address the Editor comments (see "EDITOR COMMENTS" below) in your point-by-point response.

Your paper will be maintained in active status for 7 days from the date of this letter. If we have not heard from you by Jul 16, 2021, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1:

Dr. Andra James, a leading expert in hematologic disorders of pregnancy, presents an expert review on diagnosis and management of iron deficiency anemia in pregnancy. The review is excellent. It is well written, carefully researched, and covers all the key areas on this topic. Dr. James also shares data on implementation of a successful IV iron program at her own institution. The use of IV iron in pregnancy is expected to increase significantly over the next few years, and this manuscript will be a valuable resource for providers. I do have some comments and suggestions noted below.

1. The use of alternate day dosing of iron is emphasized in the Precis, Abstract and Conclusion. While I agree it is very intriguing, I worry that the data to support this statement is very limited in pregnant women. While we should be discouraging use of oral iron 2x or 3x daily, it is unclear that every other day iron is better (or even equivalent to) daily iron in pregnancy. I enjoyed the discussion of alternate day dosing of oral iron in the review, but I don't think the data is strong enough to support its emphasis in the Precis and Main Conclusion in the absence of further studies.

2. Precis- Would avoid saying that women fail oral iron. Maybe, women who do not respond to oral iron. Or women whose anemia does not fully correct with oral iron.

3. Abstract - need units on hemoglobin >10.0 (g/dL), line 61

4. Abstract and Text- The authors state that iron deficiency anemia can be presumed in women with hemoglobin 10-11 g/dL and microcytic or normocytic anemia (lines 61-62 and lines 186-188). This statement worries me. How can the diagnosis of iron deficiency be presumed without checking iron studies and without ruling out thalassemia? The traditional teaching for microcytic anemia is to rule out hemoglobinopathy and to check ferritin, please explain why this wouldn't be done for pregnant women with mild anemia. Although practice patterns vary, I think it is important to encourage iron studies and hemoglobinopathy screening in the general OB-Gyn community prior to presuming iron deficiency anemia.

5. To elaborate on the point above, there was no mention of alpha-thal trait in the entire review. This is a diagnosis that is often missed by providers. First, there may be fetal implications to missing the diagnosis. Second, it may be difficult to fully correct anemia if the cause is alpha-thal trait and this could lead to excessive use of IV iron. I would at least add a few lines on the importance of not only the hemoglobin electrophoresis, but also testing for alpha-thal trait if hemoglobin electrophoresis is normal.

6. There was no mention of nutritional education in the paper. I would recommend adding at least 1-2 lines on the importance of dietary education on food sources of iron, folate and B12.

7. Table 1. Consider footnote for abbreviations

8. Table 1. I'm not sure where bariatric surgery might fit into the table, but it is mentioned in the review and it's an important condition to remember when thinking about anemia (and limited absorption of oral iron). Maybe can add a category for impaired absorption? This might also include pernicious anemia, since B12 deficiency can be caused by autoantibodies.

9. Line 96, consider adding placental causes like placenta previa and abruption

10. Line 103, consider listing alpha-thal and b-thal as examples of thalassemias, since they are the most common and aren't mentioned anywhere in the text.

11. Lines 201-203- please provide the reference for this systematic review

12. Line 206-207- Can the authors state why they chose 20 ng/ml at their institution? I think it is reasonable, but many experts are using 30 ng/ml. From the authors' institutional experience (Ref 62), it appears that they classify ferritin 20-100 ng/ml as mild iron deficiency. It might be worth adding a line or two to note that more work up and follow up is needed for equivocal ferritin values.

13. Line 263-266- Here it could be worth mentioning the recent RCT on Vit C supplementation for iron deficiency anemia (Li N, et al. JAMA Network Open 2020, PMID:33136134). Study showed no added benefit with Vit C.

14. Line 312- Unclear if the systematic review was cited here. Consider citing systematic review and meta-analysis by Govindappagari S, et al. Am J Perinatol 2019, PMID:30121943.

Reviewer #2:

This is a timely and important series addressing recent knowledge advancements in the understanding of iron deficiency in pregnancy. It is well-written and thorough.

Lines 127-129: It might be worth mentioning the limitations of this follow-up and particularly that methods used to assess iron supplementation on neurodevelopmental abnormalities. To refute the idea that iron supplementation may mitigate neurodevelopmental outcomes requires assessments other than I given that the associations have involved outcomes other than IQ alone.

Lines 146-149: Would be of interest to see ACOG's recommendations for screening listed here rather than the time points at which CBC is obtained during pregnancy, which the average reader is likely familiar with.

Lines 154-177: Consider revisiting this paragraph which has a different flow than the other parts of this article.

Lines 222-224: Above (lines 197) you reference that normal ferritin can be falsely reassuring. Here where you describe TIBC, it would be clinically relevant to mention the use of TIBC in diagnosis of iron deficiency when ferritin is normal.

Lines 248-249: I found the percentages and forward slashes to be difficult to read/understand.

Lines 322-323: This figure still likely overstates the risk of anaphylaxis reactions published in other studies.

Reviewer #3:

This is a clinical expert series article on anemia in pregnancy. The article is well written and contains practical advice for obstetricians. Clarifying comments below:
1. Abstract line 53-54 and Text line 79...it is confusing to say less than 10.5 OR 11.0 g/dL in the second OR third trimester in these two locations....would add, "depending on the national guideline utilized" or something like to explain why the value might be different.
2. Abstract line 58 and text line 146: Should we only be referencing what the USPSTF says here or also what ACOG recommends since this is the green journal.
3. Line 142, is there a biologic reason why C/S would be associated with anemia?
4. Screening for anemia: Should other organizations' recommendations also be referenced here?
5. Line 172-is there a citation missing here after Roux-en-Y gastric bypass.
6. Lines 193-195: What is the clinical yield of creatinine and reticulocyte count? Could one get by with ferritin alone for the diagnosis of iron deficiency anemia if low. This is also related to next discussion of iron level, TIBC and transferrin saturation...are these labs needed if the ferritin is low? Please clarify.
7. Lines 257-275: Should oral Fe supplements be eaten with or without food? Does that affect absorption?
8. Lines 299-300: CAn you recommend a preferred formulation of oral Fe. I have heard Fe gluconate is better tolerated than ferrous sulfate but I find insurance companies won't cover prescribed Fe gluconate. Can you comment on the differences or it doesn't matter? It would be helpful to have a few choices of order of preference for us to prescribe.
9. Table 4: My hospital has recently designated ferumoxytol as the preferred IV Fe formulation but I was not aware about the MRI imaging effect--can you add more to the Table to explain. Is this a permanent side effect?

EDITORIAL OFFICE COMMENTS:

1. The Editors of Obstetrics & Gynecology have increased transparency around its peer-review process, in line with efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online. Additionally, unless you choose to opt out, we will also be including your point-by-point response to the revision letter. If you opt out of including your response, only the revision letter will be posted. Please reply to this letter with one of two responses:
A. OPT-IN: Yes, please publish my point-by-point response letter.
B. OPT-OUT: No, please do not publish my point-by-point response letter.

2. Obstetrics & Gynecology uses an "electronic Copyright Transfer Agreement" (eCTA), which must be completed by all authors. When you uploaded your manuscript, each co-author received an email with the subject, "Please verify your authorship for a submission to Obstetrics & Gynecology." Please check with your coauthors to confirm that they received and completed this form, and that the disclosures listed in their eCTA are included on the manuscript's title page.

3. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions. Please access the obstetric data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-obstetrics-data-definitions and the gynecology data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-gynecology-data-definitions. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

4. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Clinical Expert Series articles should be no longer than 25 double-spaced pages (approximately 6,250 words). Figures are not considered in the final page count. Stated word limits include the title page, précis, abstract, text, tables, boxes, and figure legends, but exclude references.

5. Specific rules govern the use of acknowledgments in the journal. Please note the following guidelines:

* All financial support of the study must be acknowledged.
* Any and all manuscript preparation assistance, including but not limited to topic development, data collection, analysis, writing, or editorial assistance, must be disclosed in the acknowledgments. Such acknowledgments must identify the entities that provided and paid for this assistance, whether directly or indirectly.
* All persons who contributed to the work reported in the manuscript, but not sufficiently to be authors, must be acknowledged. Written permission must be obtained from all individuals named in the acknowledgments, as readers may infer their endorsement of the data and conclusions. Please note that your response in the journal's electronic author form verifies that permission has been obtained from all named persons.
* If all or part of the paper was presented at the Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists or at any other organizational meeting, that presentation should be noted (include the exact dates and location of the meeting).
* If your manuscript was uploaded to a preprint server prior to submitting your manuscript to Obstetrics & Gynecology, add the following statement to your title page: "Before submission to Obstetrics & Gynecology, this article was posted to a preprint server at: [URL]."

6. Provide a short title of no more than 45 characters (40 characters for case reports), including spaces, for use as a running foot.

7. The most common deficiency in revised manuscripts involves the abstract. Be sure there are no inconsistencies between the Abstract and the manuscript, and that the Abstract has a clear conclusion statement based on the results found in the paper. Make sure that the abstract does not contain information that does not appear in the body text. If you submit a revision, please check the abstract carefully.

In addition, the abstract length should follow journal guidelines. The word limit for Clinical Expert Series is 250 words. Please provide a word count.

8. Only standard abbreviations and acronyms are allowed. A selected list is available online at http://edmgr.ovid.com /ong/accounts/abbreviations.pdf. Abbreviations and acronyms cannot be used in the title or précis. Abbreviations and acronyms must be spelled out the first time they are used in the abstract and again in the body of the manuscript.

9. The journal does not use the virgule symbol (/) in sentences with words. Please rephrase your text to avoid using "and/or," or similar constructions throughout the text. You may retain this symbol if you are using it to express data or a measurement.

10. In your Abstract, manuscript Results sections, and tables, the preferred citation should be in terms of an effect size, such as odds ratio or relative risk or the mean difference of a variable between two groups, expressed with appropriate confidence intervals. When such syntax is used, the P value has only secondary importance and often can be omitted or noted as footnotes in a Table format. Putting the results in the form of an effect size makes the result of the statistical test more clinically relevant and gives better context than citing P values alone.

If appropriate, please include number needed to treat for benefits (NNTb) or harm (NNTh). When comparing two procedures, please express the outcome of the comparison in U.S. dollar amounts.

Please standardize the presentation of your data throughout the manuscript submission. For P values, do not exceed three decimal places (for example, "P = .001"). For percentages, do not exceed one decimal place (for example, 11.1%").

11. Please review the journal's Table Checklist to make sure that your tables conform to journal style. The Table Checklist

is available online here: http://edmgr.ovid.com/ong/accounts/table_checklist.pdf.

12. Please review examples of our current reference style at http://ong.editorialmanager.com (click on the Home button in the Menu bar and then "Reference Formatting Instructions" document under "Files and Resources). Include the digital object identifier (DOI) with any journal article references and an accessed date with website references. Unpublished data, in-press items, personal communications, letters to the editor, theses, package inserts, submissions, meeting presentations, and abstracts may be included in the text but not in the reference list.

In addition, the American College of Obstetricians and Gynecologists' (ACOG) documents are frequently updated. These documents may be withdrawn and replaced with newer, revised versions. If you cite ACOG documents in your manuscript, be sure the references you are citing are still current and available. Check the Clinical Guidance page at https://www.acog.org/clinical (click on "Clinical Guidance" at the top). If the reference is still available on the site and isn't listed as "Withdrawn," it's still a current document.

If the reference you are citing has been updated and replaced by a newer version, please ensure that the new version supports whatever statement you are making in your manuscript and then update your reference list accordingly (exceptions could include manuscripts that address items of historical interest). If the reference you are citing has been withdrawn with no clear replacement, please contact the editorial office for assistance (obgyn@greenjournal.org). In most cases, if an ACOG document has been withdrawn, it should not be referenced in your manuscript.

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If you choose to revise your manuscript, please submit your revision through Editorial Manager at http://ong.editorialmanager.com. Your manuscript should be uploaded as a Microsoft Word document. Your revision's cover letter should include the following:

* A confirmation that you have read the Instructions for Authors (http://edmgr.ovid.com/ong/accounts/authors.pdf), and
* A point-by-point response to each of the received comments in this letter. Do not omit your responses to the Editorial Office or Editors' comments.

If you submit a revision, we will assume that it has been developed in consultation with your co-authors and that each author has given approval to the final form of the revision.

Again, your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Jul 16, 2021, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Torri D. Metz, MD
Associate Editor, Obstetrics

2020 IMPACT FACTOR: 7.661
2020 IMPACT FACTOR RANKING: 3rd out of 83 ob/gyn journals

[redacted].

if you have any questions.

June 19, 2021

Torri Metz, MD
Associate Editor for Obstetrics
Green Journal

Dear Dr. Metz:

I am pleased to resubmit a revised version of the manuscript, "Iron Deficiency Anemia in Pregnancy." Thank you again for the invitation. I am the sole author. I received no financial support for this manuscript. The paper has not been presented elsewhere. The short title is the same as the title. The abstract has been revised to reflect the changes made in the manuscript in response to the reviewers' comments. I am opting in- please publish my point-by point responses. My responses to the reviewers' comments are below.

Sincerely,

Andra H. James, MD, MPH

REVIEWER COMMENTS:

Reviewer #1:

Dr. Andra James, a leading expert in hematologic disorders of pregnancy, presents an expert review on diagnosis and management of iron deficiency anemia in pregnancy. The review is excellent. It is well written, carefully researched, and covers all the key areas on this topic. Dr. James also shares data on implementation of a successful IV iron program at her own institution. The use of IV iron in pregnancy is expected to increase significantly over the next few years, and this manuscript will be a valuable resource for providers.

Thank you.

I do have some comments and suggestions noted below.

1. The use of alternate day dosing of iron is emphasized in the Precis, Abstract and Conclusion. While I agree it is very intriguing, I worry that the data to support this statement is very limited in pregnant women. While we should be discouraging use of oral iron 2x or 3x daily, it is unclear that every other day iron is better (or even equivalent to) daily iron in pregnancy. I enjoyed the discussion of alternate day dosing of oral iron in the review, but I don't think the data is strong enough to support its emphasis in the Precis and Main Conclusion in the absence of further studies.

The Precis has been changed to:

"First line treatment of iron deficiency anemia is oral iron. For women who do not respond, intravenous iron is safe."

In the Abstract and Main Conclusion, "support" has been changed to "suggest." The statement is now, "New evidence suggests that intermittent dosing is as effective as daily or twice daily dosing with fewer side effects."

2. Precis- Would avoid saying that women fail oral iron. Maybe, women who do not respond to oral iron. Or women whose anemia does not fully correct with oral iron.

The Precis has been changed to:

"First line treatment of iron deficiency anemia is oral iron. For women who do not respond, intravenous iron is safe."

3. Abstract - need units on hemoglobin >10.0 (g/dL), line 61

Thank you for reading so thoroughly. So noted – the manuscript has been corrected.

4. Abstract and Text- The authors state that iron deficiency anemia can be presumed in women with hemoglobin 10-11 g/dL and microcytic or normocytic anemia (lines 61-62 and lines 186-188). This statement worries me. How can the diagnosis of iron deficiency be presumed without checking iron studies and without ruling out thalassemia?

A fuller explanation is now provided in the text and the abstract has been modified:

"The patient who has mild anemia with a normal or mildly low MCV, a normal WBC and normal platelet count, likely has iron deficiency anemia. A trial of oral iron can be both diagnostic and therapeutic.(1) A follow-up hemoglobin level performed in 2 to 4 weeks should demonstrate improvement. If it does not, further evaluation, as for the patient with moderate or severe anemia, is required."

The traditional teaching for microcytic anemia is to rule out hemoglobinopathy and to check ferritin, please explain why this wouldn't be done for pregnant women with mild anemia. Although practice patterns vary, I think it is important to encourage iron studies and hemoglobinopathy screening in the general OB-Gyn community prior to presuming iron deficiency anemia.

See the response above.

5. To elaborate on the point above, there was no mention of alpha-thal trait in the entire review. This is a diagnosis that is often missed by providers. First, there may be fetal implications to missing the diagnosis. Second, it may be difficult to fully correct anemia if the cause is alpha-thal trait and this could lead to excessive use of IV iron. I would at least add a few lines on the importance of not only the hemoglobin electrophoresis, but also testing for alpha-thal trait if hemoglobin electrophoresis is normal.

The following has been added to the section on "The initial approach to the patient with anemia":

"Since the MCV is rarely less than 80 fL in mild iron deficiency anemia, the patient who has mild anemia with a very low MCV (less than 75 fL) likely has an explanation other than iron deficiency (such as previously undiagnosed thalassemia minor or sickle cell trait). A hemoglobin electrophoresis is required. The patient with sickle cell trait will be found to have hemoglobin S as well as hemoglobin A; the patient with beta thalassemia minor will be found to have elevated A2 hemoglobin (≥ 4%); but the patient with

alpha thalassemia minor will be found to have a normal hemoglobin electrophoresis and will require genetic testing to make the diagnosis."

6. There was no mention of nutritional education in the paper. I would recommend adding at least 1-2 lines on the importance of dietary education on food sources of iron, folate and B12.

So noted. The following was added to the text, " Education about adequate dietary intake of iron (as well as folate and vitamin B-12) and the dietary sources of these nutrients is important. See Box 5."

And a new Box was added:

Box 5. Recommended dietary intake of iron, folate and vitamin B12 during pregnancy(38)

Nutrient	***Source***
Iron (27 milligrams)	*Lean red meat, poultry, fish, dried beans and peas, iron-fortified cereals, prune juice*
Folic acid (600 micrograms)	*Fortified cereal, enriched bread and pasta, peanuts, dark green leafy vegetables, orange juice, beans.*
Vitamin B12 (2.6 micrograms)	*Meat, fish, poultry, milk (vegetarians should take a supplement)*

7. Table 1. Consider footnote for abbreviations

A footnote for abbreviations has been added.

8. Table 1. I'm not sure where bariatric surgery might fit into the table, but it is mentioned in the review and it's an important condition to remember when thinking about anemia (and limited absorption of oral iron). Maybe can add a category for impaired absorption? This might also include pernicious anemia, since B12 deficiency can be caused by autoantibodies.

This is an excellent suggestion. In Table 1, a category was added under "Decreased RBC Production," just below "Nutrient deficiency" for "Impaired absorption." Under that heading was added "Bariatric surgery" and "Intrinsic factor deficiency (surgical, autoimmune – as in pernicious anemia)." In the category of Mixed mechanisms, under the heading of Autoimmune disease was also added "impaired absorption."

9. Line 96, consider adding placental causes like placenta previa and abruption

Placental causes were added.

10. Line 103, consider listing alpha-thal and b-thal as examples of thalassemias, since they are the most common and aren't mentioned anywhere in the text.

Alpha and beta thalassemia have been listed.

11. Lines 201-203- please provide the reference for this systematic review

Thank you. The previous oversight has been corrected and the reference has been added.

12. Line 206-207- Can the authors state why they chose 20 ng/ml at their institution? I think it is reasonable, but many experts are using 30 ng/ml.
We appreciate that there is a range of thresholds used and that the new ACOG threshold is 30 mcg/L

I have expounded on our choice of 20 ng/mL:

While our institution uses a threshold of 20 ng/mL, this is a soft threshold with any level less than 100 ng/mL being considered at least mild iron deficiency. Especially if the ferritin level is equivocal, confirmation of the diagnosis of iron deficiency anemia with additional laboratory testing is needed.

From the authors' institutional experience (Ref 62), it appears that they classify ferritin 20-100 ng/ml as mild iron deficiency. It might be worth adding a line or two to note that more work up and follow up is needed for equivocal ferritin values.

The following has been added to the text:

"Especially if the ferritin level is equivocal, confirmation of the diagnosis of iron deficiency anemia with additional laboratory testing is needed."

13. Line 263-266- Here it could be worth mentioning the recent RCT on Vit C supplementation for iron deficiency anemia (Li N, et al. JAMA Network Open 2020, PMID:33136134). Study showed no added benefit with Vit C.

Thank you. This study has now been cited and the following statement has been added to the text:

"In a recently published randomized clinical trial, oral iron supplements alone were equivalent to oral iron supplements plus vitamin C in improving hemoglobin levels."

14. Line 312- Unclear if the systematic review was cited here. Consider citing systematic review and meta-analysis by Govindappagari S, et al. Am J Perinatol 2019, PMID:30121943.

The systematic review that was quoted was not properly cited. This error has been corrected. Also, the systematic review above has now been quoted and cited as well. Thank you.

"A recent systematic review found that intravenous had fewer side effects than oral iron."

Reviewer #2:

This is a timely and important series addressing recent knowledge advancements in the understanding of iron deficiency in pregnancy. It is well-written and thorough.

Thank you.

Lines 127-129: It might be worth mentioning the limitations of this follow-up and particularly that methods used to assess iron supplementation on neurodevelopmental abnormalities. To refute the idea that iron supplementation may mitigate neurodevelopmental outcomes requires assessments other than I given that the associations have involved outcomes other than IQ alone.

This segment has been rewritten and now states:

"In theory, if iron deficiency anemia causes such adverse outcomes [behavioral and neurodevelopmental abnormalities], then iron supplementation should reduce the risk of behavioral and neurodevelopmental abnormalities. One randomized trial, which examined intelligence quotient (IQ) and behavior at 4 years of age, did not find a benefit of iron supplementation.(25) Other studies, however, as well as assessments other than IQ and behavior, would be required to support or refute or a benefit of iron supplementation".

Lines 146-149: Would be of interest to see ACOG's recommendations for screening listed here rather than the time points at which CBC is obtained during pregnancy, which the average reader is likely familiar with.

The following has been added to the text:

"The American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin on Anemia in Pregnancy recommends screening for anemia with a CBC in the first trimester and again at 24 0/7 to 28 6/7 weeks gestation."

Lines 154-177: Consider revisiting this paragraph which has a different flow than the other parts of this article.

This paragraph has been rewritten in a different voice.

Lines 222-224: Above (lines 197) you reference that normal ferritin can be falsely reassuring. Here where you describe TIBC, it would be clinically relevant to mention the use of TIBC in diagnosis of iron deficiency when ferritin is normal.

This is an excellent suggestion. These lines have been rewritten and now read:

"Transferrin saturation is the ratio of serum iron to the TIBC divided by 100 which represents the percentage of transferrin's iron-binding sites being occupied by iron. A low transferrin saturation is indicative of iron deficiency and can be used in the diagnosis of iron deficiency when ferritin is normal."

Lines 248-249: I found the percentages and forward slashes to be difficult to read/understand.

The slashes were removed. The text now reads:

"Sources of iron for the prescription/nonprescription products were ferrous fumarate in 44% of prescription and 49% of nonprescription products; amnio acid chelates in 14% of prescription and 31% of nonprescription products; carbonyl or elemental iron in 19% of prescription and 5% of nonprescription products; ferrous gluconate in 7 % of prescription and 1% of nonprescription products; and another or

unspecified chemical form in 16% of prescription and 14% of nonprescription products. None of the prenatal vitamins used ferrous sulfate as the source of iron."

Lines 322-323: This figure still likely overstates the risk of anaphylaxis reactions published in other studies.

A risk of less than 1/1000 with contemporary intravenous iron formulations as published by Wang et al in JAMA (2015), is the best data we have.

Reviewer #3:

This is a clinical expert series article on anemia in pregnancy. The article is well written and contains practical advice for obstetricians.

Thank you.

Clarifying comments below:

1. Abstract line 53-54 and Text line 79...it is confusing to say less than 10.5 OR 11.0 g/dL in the second OR third trimester in these two locations....would add, "depending on the national guideline utilized" or something like to explain why the value might be different.

These lines have been rewritten in the abstract and the main text:

In pregnancy, a hemoglobin concentration of less than 11.0 g/dL in the first trimester and less than 10.5 or 11.0 g/dL in the second or third trimester (depending on the guideline used) is considered anemia.

Additionally in the main text, instead of "Box 1," it now reads, "See Box 1 for the definitions of anemia according to various guidelines."

2. Abstract line 58 and text line 146: Should we only be referencing what the USPSTF says here or also what ACOG recommends since this is the green journal.

The abstract now reads:

While the United States Preventive Services Task Force does not recommend routine screening for anemia in pregnancy, ACOG recommends screening for anemia with a CBC in the first trimester and again at 24 0/7 to 28 6/7 weeks gestation.

And the text now includes:

The American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin on Anemia in Pregnancy recommends screening for anemia with a CBC in the first trimester and again at 24 0/7 to 28 6/7 weeks gestation.

3. Line 142, is there a biologic reason why C/S would be associated with anemia?

As stated in the text, "Anemia is present in multiple conditions that increase the risk of adverse outcomes such as hemoglobinopathies, infections, and autoimmune disease. Anemia may be a contributor to adverse fetal and neonatal outcomes or may merely accompany these conditions that negatively impact fetal and neonatal well-being." The increased risk of cesarean is likely a reflection of the fact that anemia is present in these multiple conditions that increase the risk of adverse outcomes including the risk of cesarean.

4. Screening for anemia: Should other organizations' recommendations also be referenced here?

ACOG has been added.

5. Line 172-is there a citation missing here after Roux-en-Y gastric bypass.

Yes, the citation was missing. Thank you for noticing. It has been added.

6. Lines 193-195: What is the clinical yield of creatinine and reticulocyte count?

This is a good question. The clinical yield for any of these studies is unknown. Serum ferritin likely has the highest clinical yield, however, and this has been added to the text.

Could one get by with ferritin alone for the diagnosis of iron deficiency anemia if low.

Line 196 was amended from, "Low serum ferritin is both highly sensitive and highly specific for iron deficiency in pregnancy(30)," to, "Low serum ferritin is both highly sensitive and highly specific for iron deficiency in pregnancy(30) and may be considered diagnostic.(1)

This is also related to next discussion of iron level, TIBC and transferrin saturation...are these labs needed if the ferritin is low? Please clarify.

The following clarification was added:

"When ferritin is low, no other laboratory testing may be necessary."

7. Lines 257-275: Should oral Fe supplements be eaten with or without food? Does that affect absorption?

The following was added to the text:

Absorption of iron from oral supplements may be improved when taken between meals or at bedtime, but there are few data. One study found that serum ferritin levels were slightly, but statistically

significantly higher in subjects who took oral iron supplements between meals or at bedtime, rather than with meals.(46)

8. Lines 299-300: CAn you recommend a preferred formulation of oral Fe. I have heard Fe gluconate is better tolerated than ferrous sulfate but I find insurance companies won't cover prescribed Fe gluconate. Can you comment on the differences or it doesn't matter? It would be helpful to have a few choices of order of preference for us to prescribe.

To address these important questions and concerns, without being too directive, here is what has been added to the text:

The tolerability of oral iron, however, is likely a function of the amount of elemental iron in a given dose – the lower the amount of elemental iron per tablet, the better tolerated the formulation. Oral iron formulations and their amount of elemental iron per tablet size are listed in Box 6.

9. Table 4: My hospital has recently designated ferumoxytol as the preferred IV Fe formulation but I was not aware about the MRI imaging effect--can you add more to the Table to explain. Is this a permanent side effect?

The following footnote was added to Table 4:

"Ferumoxytol was originally developed as an MRI contrast agent. Its image-enhancing effects may be present for 72 hours or more after administration."