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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.*

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

**Date:** 12/08/2022
**To:** "Mitchell D. Creinin" [redacted]
**From:** "The Green Journal" em@greenjournal.org
**Subject:** Your Submission ONG-22-1910

RE: Manuscript Number ONG-22-1910

Heavy Menstrual Bleeding Treatment with a Levonorgestrel 52 mg Intrauterine Device

Dear Dr. Creinin:

Thank you for sending us your work for consideration for publication in Obstetrics & Gynecology. Your manuscript has been reviewed by the Editorial Board and by special expert referees. The Editors would like to invite you to submit a revised version for further consideration.

If you wish to revise your manuscript, please read the following comments submitted by the reviewers and Editors. Each point raised requires a response, by either revising your manuscript or making a clear argument as to why no revision is needed in the cover letter.

To facilitate our review, we prefer that the cover letter you submit with your revised manuscript include each reviewer and Editor comment below, followed by your response. That is, a point-by-point response is required to each of the EDITOR COMMENTS (if applicable), REVIEWER COMMENTS, and STATISTICAL EDITOR COMMENTS (if applicable) below.

The revised manuscript should indicate the position of all changes made. Please use the "track changes" feature in your document (do not use strikethrough or underline formatting).

Your submission will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by 12/29/2022, we will assume you wish to withdraw the manuscript from further consideration.

EDITOR COMMENTS:

Please note the following:

1. Please address reviewer comments regarding no difference in outcome based on BMI and parity, but lack of information on power to detect a difference between groups based on these variables.

2. If comparing outcomes by BMI was not an a priori primary objective of the study, please make it clear it was exploratory

3. Please revise the conclusion and discussion/limitations section to reflect above. Thank you.

Please also note:

* Help us reduce the number of queries we add to your manuscript after it is revised by reading the Revision Checklist at https://journals.lww.com/greenjournal/Documents/RevisionChecklist_Authors.pdf and making the applicable edits to your manuscript.

REVIEWER COMMENTS:

Reviewer #1: This study adds knowledge regarding use of the levonorgestrel IUD for heavy menstrual bleeding in important subpopulations of women.
- Lines 92 and 115: A serum sample was drawn to "coordinate with the menstrual products." It is unclear by the wording as to what this process looks like.
- Line 121: The option to have the device removed after the treatment phase is described. Where are the data presented?
- Lines 164 and 214: The discontinuation/expulsion data sentences are muddy as written. Perhaps, on Line 164, the term "Overall," could start the sentence. Perhaps, on Line 214, "discontinued early due to IUD-related complaints, including expulsion" would be clearer and lead into the next sentence.
- Line 235: Data regarding endometrial findings were not noted.

Reviewer #2: The authors present a single group assignment open label study to assess heavy menstrual bleeding treatment with levonorgestrel 52 mg intrauterine device. The study was well designed and appears to be properly carried out. However I have the following concerns;

1. There are over 25 randomized control trials looking at this question, many of which compared LNG-IUS with another form of treatment ( PMID:32529637), all of which found a 90% decrease in menstrual bleeding with IUS. The lack of a comparison treatment in the current study detracts from its clinical value. I failed to see the need for another trial, other than to achieve FDA approval for this IUS, that is basically identical to the Mirena LNG-IUS.

2. The authors suggest that they have shown that BMI is not a factor in the success of LNG-IUS control of HMB. I am concerned because the study was not design to look at this question nor was it listed as a secondary outcome in the original NCT 03642210. How confident were the authors in making this statement, what was the power calculation, did they control for other co variants in the above and below 30 BMI cohorts. Since the FDA has approved the Mirena IUS for HMB up to a BMI of 35, should this not have been the threshold for suggesting it is acceptable in class 2 obese individuals? If 25% of the subjects had BMI greater than 35, they should have been specifically compared to those less than 35 BMI, I doubt you would have adequate power to make this comparison as stated above.

3. The same argument holds for parity, there have been many studies that have been performed in individuals that were multiparous. How confident were the authors making this statement the parity was not effect? What was the power calculation? I noted no adjustment for other co variants?

4. The other interesting point in this paper was the high expulsion rate, which was 2 fold increase what has been reported in the literature. The authors stated that all the expulsed IUS were in patients with a BMI of greater than 35 (25% of subjects). Was it statistically significant when you compared those with an expulsed IUS vs those retained IUS? Did you control for other variables (amount of bleeding, uterine cavity, comorbidities, parity, etc). Once again your study was not designed to answer this question nor was it powered to address this issue.

5. In the discussion, please include a more appropriate review of the current literature and the limitations of your paper on the effect of BMI/parity/expulsion rate as a secondary outcome.

6. Do not report extensive list of results in the text . Only include significant an appropriate results in the text. Tables are more appropriate for these reporting this data.

In addition:
- Ln 37-41: This section is not necessary. Please keep your introduction focused on the point of the paper and a more appropriate review of the literature is needed (especially in discussion).
- Ln 132: I am concerned about you evaluating outcomes in participants with at least 1 follow-up assessment? How many patients did this include with only 1 assessment?
- Ln 230: The authors need to show more convincing evidence, than stating the data clearly show that expulsion risk in patients with subjective HMB…

Reviewer #3: The authors report the findings of a well-designed, industry sponsored, observational study evaluating a levonorgestrel 52mg intrauterine device (IUD) placed in 105 women with heavy menstrual bleeding. This was a prospectively conducted study performed at 29 US centers. The authors used rigorous criteria to define HMB with precise measurements for measuring the amount of blood loss using the gold standard measurement method of alkaline hematin testing. The participants were appropriately evaluated to ensure that the etiology for the HMB was AUB-E using the PALM-COIEN criteria. Importantly, the authors included patients in higher BMI categories, nulliparous patients and patients not desiring the IUD for contraception. The study enrolled 45% of patients categorized as obese (similar to the expected percentage of obese women in the US) and 28% were nulliparous and the authors reported similar reductions in blood loss for obese and nulliparous women of >90% over 6 months compared to baseline amounts for most IUD users. The study would be expected to be generalizable to a US population because 35% of patients were from minority groups and included the higher numbers of obese and nulliparous women. There was a higher-than-expected rate of discontinuation and expulsion in the IUD users with HMB and does provide information that can be used by clinicians to counsel patients using an IUD for these purposes. The outcomes of the study are appropriately presented, and the conclusions are appropriate for the data presented.

STATISTICAL EDITOR COMMENTS:
Table 1: Should include a column of the 16 who did not have follow-up to illustrate any differences vs the analyzed group.

Table 2: Should separate the primary outcome from the secondary, subset analyses. The study was not powered to evaluate differences between subsets. Based on the counts for BMI strata and a rate = 94% for the < 30 kg/m² group, and assuming power = 80% and alpha = 0.05, the discernable alternative rate would have to be < 68%. So, the comparison is NS, but underpowered to generalize that there is no difference. For parity, the math is similar with a

discernible alternative again < 68%. Should simply show the proportions and their CIs, but not generalize from these data that the result in the subsets are NS different.

Table 3: Same as in Table 2, cannot generalize the NS comparisons by BMI or parity. NS but underpowered.

Table 4: Need to include some measure of variability (IQR or range).

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Sincerely,
Vivian W. Sung, MD, MPH
Deputy Editor, Gynecology--Elect

The Editors of Obstetrics & Gynecology

_____

UCDAVIS HEALTH

Department of Obstetrics and Gynecology

Division of Family Planning

4860 Y Street, Suite 2500
Sacramento, CA 95817
[redacted]

January 9, 2023

The Editors
*Obstetrics & Gynecology*
409 12th Street, SW
Washington, DC 20024-2188

Re: Manuscript #ONG-22-1910

To the Editor:

Enclosed are the responses to the reviewers' and editors' comments for the manuscript titled "Heavy Menstrual Bleeding Treatment with a Levonorgestrel 52 mg Intrauterine Device." All of the comments were incredibly constructive and helped improve the manuscript. We have requested to keep some of the statistical considerations in regard to points made by the statistical editor, as we feel we have addressed these limitations in the manuscript. If the editor still feels this information needs to be removed, we are happy to address these points again.

The Sponsor and authors have adhered to the GPP3 guideline for this manuscript. All authors have contributed to this revised manuscript and agree on this submitted version. The comments are addressed as outlined below. The manuscript is submitted with changes marked as well as a clean version; the line numbers refer to the clean version.

Required submission in the original cover letter has not been reported in this reply letter. Thank you for your further consideration of our manuscript.

Sincerely,

Mitchell D. Creinin, MD
Professor
Director, Complex Family Planning Fellowship

EDITOR'S COMMENTS:

1. Please address reviewer comments regarding no difference in outcome based on BMI and parity, but lack of information on power to detect a difference between groups based on these variables.

   RESPONSE: Please see our response to comments #2, 3 and 10.

2. If comparing outcomes by BMI was not an a priori primary objective of the study, please make it clear it was exploratory.

   RESPONSE: These outcomes were considered as part of the statistical plan and are detailed in the clinical study report submitted to the FDA. The study sample was estimated to meet the primary outcome for the entire population and not these subpopulations, although they are of significant interest. Per your recommendation, we have changed the wording to reflect that these secondary evaluations are exploratory and also clarified the sample size was based on expected outcomes for the entire study cohort.

   Lines 18-19:
   *Old text: We compared outcomes by BMI and parity using Wilcoxon Rank-Sum Test.*
   *New text: We evaluated exploratory outcomes of differences in blood loss changes by BMI and parity using Wilcoxon Rank-Sum Test.*

   Lines 141-143:
   *Old text: For this analysis, we also assessed median absolute change in blood loss overall as well as in subgroups by obesity status (BMI < and ≥30 kg/m2) and parity (nulliparous vs parous) using Wilcoxon Rank-Sum Test.*
   *New text: We assessed median absolute change in blood loss overall, as well as exploratory evaluations in subgroups by obesity status and parity, using Wilcoxon Rank-Sum Test.*

   Lines 145-146:
   *Old text: The sample size was estimated based on expected successful treatment rate of ≥80% such that the lower bound...*
   *New text: The sample size was estimated based on expected successful treatment rate of ≥80% for the entire study cohort such that the lower bound…*

3. Please revise the conclusion and discussion/limitations section to reflect above. Thank you.

   RESPONSE: We amended the conclusion of the abstract and added statements in the strengths/limitations paragraph and concluding paragraph.

   Lines 32-33 (Abstract):
   *Old text: This levonorgestrel 52mg IUD reduces blood loss >90% over six months compared to baseline for most users with HMB regardless of BMI and parity.*
   *New text: This levonorgestrel 52mg IUD reduces blood loss >90% over six months compared to baseline for most users with HMB.*

Lines 238-242:

*Old text: The demographics of the study population include relatively high proportions of minority, obese and nulliparous participants, meaning the results are likely widely applicable. This study used thorough evaluations…*

*New text: The demographics of the study population include relatively high proportions of minority, obese and nulliparous participants, meaning the results are likely widely applicable. Still, the number of obese and nulliparous participants were only sufficient for exploratory analyses in these populations since the overall study was underpowered for these specific assessments. This study used thorough evaluations…*

Lines 256-259:

*Old text: Our results will, for the first time, provide clinicians and patients with the knowledge that efficacy is maintained in patients with these characteristics and expand the generalizability of the levonorgestrel 52 mg IUD as a highly effective HMB treatment.*

*New text: Our results provide clinicians and patients with the knowledge that efficacy is maintained in populations that include patients with these characteristics and expand the generalizability of the levonorgestrel 52 mg IUD as a highly effective HMB treatment.*

4. Help us reduce the number of queries we add to your manuscript after it is revised by reading the Revision Checklist at https://nam12.safelinks.protection.outlook.com/?url=https%3A%2F%2Fjournals.lww.com%2Fgreenjournal%2FDocuments%2FRevisionChecklist_Authors.pdf&data=05%7C01%7Cmdcreinin%40ucdavis.edu%7C0acf4a69be194942118908dad95c1a1b%7Ca8046f6466c04f009046c8daf92ff62b%7C0%7C1%7C638061286844736742%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C3000%7C%7C%7C&sdata=93TkGMDgLWGGumfNrQPDlKfzOzbtiEA5q4Fi51NV6cM%3D&reserved=0 and making the applicable edits to your manuscript.

RESPONSE: We reviewed the information and made the following edits:

Cover letter: We have added acknowledgement that the Sponsor and authors have adhered to the GPP3 guideline for this manuscript.

Title page: The role of the funder was added. This information was already in the text immediately before the Results section. We have left the information in the text as well.

Central IRB name added (line 65); please note that specific study site locations are not named (they are available publicly through ClinicalTrials.gov).

Percentages for original results have been amended to one decimal place throughout the manuscript.

Primacy claims are removed (from line 256).

Tables are now formatted with a table function.

Authors' Data Sharing Statement added.

REVIEWER COMMENTS:

Reviewer #1

5. Lines 92 and 115: A serum sample was drawn to "coordinate with the menstrual products." It is unclear by the wording as to what this process looks like.

RESPONSE: We apologize for the apparent lack of clarity. Because hemoglobin levels vary from person to person, blood from the participant is needed to standardize the assay for the menstrual products obtained for that person. We do not feel that adding that much detail is needed for this publication as AH testing is commonly used in gynecologic bleeding studies and the information widely available, including online at https://kcasbio.com/wp-content/uploads/2013/11/KCAS-Measurement-of-blood-loss-by-Alkaline-Hematin.pdf. We have modified the initial description to simplify the initial explanation.

Lines 91-95:

*Old text: Screening cycle assessments occurred in up to three cycles. Participants were scheduled to attend a visit within 5 days of the end of menses to provide collected menstrual products and have a serum sample obtained to coordinate with the menstrual products for alkaline hematin testing, although the visit could occur up to 21 days after menses.*

*New text: Screening cycle assessments occurred in up to three cycles during which participants collected menstrual products for alkaline hematin testing. Participants were scheduled to attend a visit within 5 days of the end of menses to provide collected menstrual products and have a serum sample obtained for alkaline hematin blood loss calculations, although the visit could occur up to 21 days after menses.*

6. Line 121: The option to have the device removed after the treatment phase is described. Where are the data presented?

RESPONSE: The number who discontinued after completing 6 cycles of IUD use was not a study outcome; as such, we did not collect the reasons for discontinuation should the participant have chosen to do so. Eight participants chose to have the IUD removed after completing 6 cycles of use. Because we do not know if the choice to have removal was related to an adverse event, desiring pregnancy, or some other reason, including that information does not provide accurate additional data.

7. Lines 164 and 214: The discontinuation/expulsion data sentences are muddy as written. Perhaps, on Line 164, the term "Overall," could start the sentence. Perhaps, on Line 214, "discontinued early due to IUD-related complaints, including expulsion" would be clearer and lead into the next sentence.

RESPONSE: Thank you for your comment. To provide clarity, we have amended the first sentence. The second question reads “Although bleeding decreased substantially in participants with follow-up bleeding data, 14 (13%) discontinued early due to expulsion or IUD-related complaints (Figure 1).” We believe this sentence is most accurate as written. Our goal is to specify that 14 participants discontinued for expulsion or a specific complaint related to the IUD, such as cramping. Both the way the reviewer suggested writing the sentence and our current structure are correct, and we prefer to leave the sentence written as is based on the points we want to emphasize.

Lines 165-166:

*Old text: Twenty-three (22%) participants discontinued expulsion (n=5, 5%), bleeding complaint (n=4, 4%)…*

*New text: Twenty-three (21.9%) participants discontinued for reasons of expulsion (n=5, 4.8%), bleeding complaint (n=4, 3.8%)…*

8. Line 235: Data regarding endometrial findings were not noted.

RESPONSE: We did not have any endometrial findings to present other than baseline screening criteria that were used to ensure no exclusions were met. Participants who used the IUD did not have any direct endometrial outcomes assessed.

Reviewer #2:

9. There are over 25 randomized control trials looking at this question, many of which compared LNG-IUS with another form of treatment ( PMID:32529637), all of which found a 90% decrease in menstrual bleeding with IUS. The lack of a comparison treatment in the current study detracts from its clinical value. I failed to see the need for another trial, other than to achieve FDA approval for this IUS, that is basically identical to the Mirena LNG-IUS.

   RESPONSE: Thank you for your comment. The Cochrane review includes many randomized trials that evaluate the levonorgestrel 52 mg IUD for HMB, as you point out. You are also correct that despite all of these studies, the FDA still required this study for this specific IUD to be approved using alkalin hematin testing. We recognize that this is "just another study" which is why we focused on the unique aspects related to the population enrolled, specifically BMI and parity. As we point out in the paper, prior studies performed in a similar setting to this study do not include women of high BMI or nulliparity. The studies included in the Cochrane review included both those that used alkalin hematin evaluations and pictorial bleeding assessment chart scores. Some of the studies included women scheduled for hysterectomy which are likely different than the population treated in this study. Most studies were performed in developing countries with population characteristics that differ significantly from the populations served by clinicians who read this journal. For these reasons, we believe that this work has some unique value above and beyond meeting FDA requirements for approval.

10. The authors suggest that they have shown that BMI is not a factor in the success of LNG-IUS control of HMB. I am concerned because the study was not design to look at this question nor was it listed as a secondary outcome in the original NCT 03642210. How confident were the authors in making this statement, what was the power calculation, did they control for other co variants in the above and below 30 BMI cohorts. Since the FDA has approved the Mirena IUS for HMB up to a BMI of 35, should this not have been the threshold for suggesting it is acceptable in class 2 obese individuals? If 25% of the subjects had BMI greater than 35, they should have been specifically compared to those less than 35 BMI, I doubt you would have adequate power to make this comparison as stated above.

    RESPONSE: Thank you for your comment. Please see our responses to Editor's Points #2 and 3. Obesity is standardly defined by BMI of 30 $kg/m^2$ which is why we present the data primarily in this manner. We have added information related to outcomes in an online appendix based on BMI with groupings of 35 $kg/m^2$ or less vs. more than 35 $kg/m^2$. We chose an online appendix since the numbers are smaller (as you point out) and because the outcomes are not very different than using a cut-off of 30 $kg/m^2$. We made an additional change based on your comment to Table 1 in which we now present the number of participants with BMI that exceeded 35 $kg/m^2$ and not equal to or more than 35 $kg/m^2$.

    *New Online Appendix 3*

Appendix 3. Comparisons of treatment success and change in blood loss over 6 cycles in participants with BMI ≤35 kg/m$^2$ and > 35 kg/m$^2$ in a Phase 3 study evaluating levonorgestrel 52 mg intrauterine device for heavy menstrual bleeding treatment

a. Treatment Success

| | Number[a] | Treatment success[b] | P-value[c] |
|---|---|---|---|
| Body Mass Index (kg/m$^2$) | | | |
| ≤ 35 | 65 | 60 (92.3%, 95% CI 85.8-98.8%) | 0.68 |
| > 35 | 24 | 21 (87.5%, 95% CI 74.3-100.0%) | |

b. Change in Bleeding Outcome

| | Baseline[d] | | Cycle 6 | | Median Decrease[e] | P-value[f] |
|---|---|---|---|---|---|---|
| | Number | Blood loss (mL)[g] | Number | Blood loss (mL)[g] | | |
| Body Mass Index (kg/m$^2$) | | | | | | |
| ≤ 35 | 60 | 136.6 | 60 | 3.8 | 97.4% | 0.33 |
| | | (IQR 111.5-191.7) | | (IQR 0.0-10.9) | (IQR 89.9-100%) | |
| > 35 | 21 | 171.2 | 21 | 2.5 | 99.0% | |
| | | (IQR 111.7-192.9) | | (IQR 0.0-7.5) | (IQR 94.9-100%) | |

IQR: interquartile range

[a] Participants with any follow-up bleeding evaluations

[b] Menstrual blood loss during treatment <80 mL and >50% reduction from baseline during the last 28-day cycle of treatment (Cycle 3 or Cycle 6).

[c] Fisher exact test

[d] Only including 81 participants with Cycle 6 outcome

[e] Baseline to Cycle 6 only for participants with Cycle 6 outcome

[f] Comparing median decrease from baseline to Cycle 6 only for participants with Cycle 6 outcome (Wilcoxon Rank-Sum Test)

[g] median

Lines 180-182:
*Old text: Treatment success rates did not differ by obesity status or parity (Table 2).*
*New text: Treatment success rates did not differ by obesity status (BMI < and ≥30 kg/m$^2$) or parity (Table 2) or when evaluating outcomes by BMI ≤ and >35 kg/m$^2$ (Online Appendix 3).*

Lines 186-188:
*Old text: Median decrease in blood loss by cycle 6 did not differ by obesity status or parity (Table 3).*
*New text: Median decrease in blood loss by cycle 6 did not differ by obesity status or parity (Table 3) or when evaluating outcomes by BMI ≤ and >35 kg/m$^2$ (Online Appendix 3).*

11. The same argument holds for parity, there have been many studies that have been performed in individuals that were multiparous. How confident were the authors making this statement the parity was not effect? What was the power calculation? I noted no adjustment for other co variants?

RESPONSE: We have changed the wording to exploratory as suggested by the Editor (see responses #2 and 3). With relatively small numbers, as you point out, a multivariable regression is inappropriate, especially given the effect size is so high and the same regardless of parity (or BMI).

12. The other interesting point in this paper was the high expulsion rate, which was 2 fold increase what has been reported in the literature. The authors stated that all the expulsed IUS were in patients with a BMI of greater than 35 (25% of subjects). Was it statistically significant when you compared those with an expulsed IUS vs those retained IUS? Did you control for other variables (amount of bleeding, uterine cavity, comorbidities, parity, etc). Once again your study was not designed to answer this question nor was it powered to address this issue.

RESPONSE: The expulsion rate is high as would be expected when a levonorgestrel IUD is used for HMB. Given the sample size, the rate is not significantly higher than other studies (and we have added 95% confidence intervals to demonstrate as such). Obviously, the study was not powered to have enough expulsions to do a multivariable analysis which would be inappropriate statistically here. However, we have learned much more about IUD expulsion with contemporary literature as compared to when the Mirena HMB study was performed. We believe the discussion appropriately addresses these issues.

Line 189:
*Old text: Nine (9%) participants experienced expulsion…*
*New text: Nine (8.6%, 95% CI 3.2-13.9%) participants experienced expulsion…*

13. Ln 37-41: This section is not necessary. Please keep your introduction focused on the point of the paper and a more appropriate review of the literature is needed (especially in discussion).

RESPONSE: Thank you for your comment. Since clinicians and leading medical organizations refer to HMB based on patient experience, and this may differ from how regulatory agencies approach HMB, we felt this information was important and relevant. Additionally, the information provides background for the reader related to the use of 80 mL as the defining amount of blood loss for this study, as required by the FDA.

14. Ln 132: I am concerned about you evaluating outcomes in participants with at least 1 follow-up assessment? How many patients did this include with only 1 assessment

RESPONSE: Thank you for your comment. The treatment portion of the study had only two follow-up assessments, at cycles 3 and 6 after placement, with the 6-cycle assessment as the primary outcome. The study plan as designed and desired by the FDA was to include participants with at least one assessment such that those with only a 3-cycle assessment would have that value carried forward as the "final" outcome and those with only a 6-cycle assessment would have the final outcome value identified. In essence, this one assessment requirement, which was the same in the Mirena HMB study, would more likely serve to decrease the effect if many participants had just a 3-cycle value carried forward. As is demonstrated in Figure 1, there was one participant who did not supply bleeding data at cycle 3 and continued in the study to cycle 6. Additionally, there were 9 people who had visit 3 values and discontinued between cycles 3 and 6 or did not provide a bleeding assessment at cycle 6. These 9 cycle 3 values were carried forward as the final outcome values. So, this information is present in the manuscript already and is does not deflate the outcome findings.

15. Ln 230: The authors need to show more convincing evidence, than stating the data clearly show that expulsion risk in patients with subjective HMB…

    RESPONSE: Please see the response to comment #12.

Reviewer #3:

16. The authors report the findings of a well-designed, industry sponsored, observational study evaluating a levonorgestrel 52mg intrauterine device (IUD) placed in 105 women with heavy menstrual bleeding. This was a prospectively conducted study performed at 29 US centers. The authors used rigorous criteria to define HMB with precise measurements for measuring the amount of blood loss using the gold standard measurement method of alkaline hematin testing. The participants were appropriately evaluated to ensure that the etiology for the HMB was AUB-E using the PALM-COIEN criteria. Importantly, the authors included patients in higher BMI categories, nulliparous patients and patients not desiring the IUD for contraception. The study enrolled 45% of patients categorized as obese (similar to the expected percentage of obese women in the US) and 28% were nulliparous and the authors reported similar reductions in blood loss for obese and nulliparous women of >90% over 6 months compared to baseline amounts for most IUD users. The study would be expected to be generalizable to a US population because 35% of patients were from minority groups and included the higher numbers of obese and nulliparous women. There was a higher-than-expected rate of discontinuation and expulsion in the IUD users with HMB and does provide information that can be used by clinicians to counsel patients using an IUD for these purposes. The outcomes of the study are appropriately presented, and the conclusions are appropriate for the data presented.

    RESPONSE: Thank you for the comments.

STATISTICAL EDITOR'S COMMENTS:

17. Table 1: Should include a column of the 16 who did not have follow-up to illustrate any differences vs the analyzed group.

RESPONSE: We have added an additional column to Table 1 with this information. We opted not to perform any statistical testing due to the extremely small numbers within subgroups.

18. Table 2: Should separate the primary outcome from the secondary, subset analyses. The study was not powered to evaluate differences between subsets. Based on the counts for BMI strata and a rate = 94% for the < 30 kg/m² group, and assuming power = 80% and alpha = 0.05, the discernable alternative rate would have to be < 68%. So, the comparison is NS, but underpowered to generalize that there is no difference. For parity, the math is similar with a discernible alternative again < 68%. Should simply show the proportions and their CIs, but not generalize from these data that the result in the subsets are NS different.

    RESPONSE: We agree with the statistical reviewer that we were underpowered which the Editor and Reviewer #2 pointed out clearly. However, we do not feel that negates showing the results of the statistical testing. We believe that the recommendations by the Editor and Reviewer #2 to clarify this limitation in the Discussion provides context for the reader. Given the paucity of data in these populations for studies that are extremely difficult to do, we kindly request that the p-values remain.

19. Table 3: Same as in Table 2, cannot generalize the NS comparisons by BMI or parity. NS but underpowered.

    RESPONSE: See response to #18.

20. Table 4: Need to include some measure of variability (IQR or range).

    RESPONSE: We have added IQR values to the table.

Additional Changes:

1. We updated word counts and number of appendices on the Title Page.

2. Lines 23-24 (Abstract): the blood loss values were corrected to match the text (in addition to changing the percentages to one decimal point).

    *Old text: Participants had median absolute blood loss decreases at cycles three(n=86) and six(n=81) of 93%(IQR 82-98%) and 97%(IQR 90-100%), respectively.*
    *New text: Participants had median absolute blood loss decreases at cycles three(n=86) and six(n=81) of 93.3%(IQR 86.1-97.7%) and 97.6%(IQR 90.4-100%), respectively.*

3. Lines 24-25 (Abstract): the number of non-obese and obese participants were corrected to match the main text (in addition to changing the percentages to one decimal point).

    *Old text: At cycle six, non-obese(n=46) and obese(n=35) participants...*
    *New text: At cycle six, non-obese(n=43) and obese(n=38) participants...*

4. Line 40 (Introduction): a typographical error related to reference presentation was corrected

    *Old text: …with a blood loss of 80 mL or more considered HMB (Halberg-2).*
    *New text: ...with a blood loss of 80 mL or more considered HMB.[2]*

5. Lines 176-177 (Results): a typographical error related to success rates was corrected.

   *Old text: ...81% (73-88%) of the 99 participants excluding those with no outcomes…*
   *New text: ...81.8% (95% CI 74.2-89.4%) of the 99 participants excluding those with no outcomes…*

6. Line 209 (Discussion): a typographical error related to reporting previously published data was corrected.

   *Old text: ...in a parous population with a mean BMI of 27.21 ± 3.9 kg/$m^2$.*
   *New text: ...in a parous population with a mean BMI of 27.2 ± 3.9 kg/$m^2$.*

7. Line 221 (Discussion): we simplified the text.

   *Old text: The expulsion rate of 9% within 6 cycles is much higher than is typically seen…*
   *New text: The expulsion rate of 9% within 6 cycles is higher than is typically seen…*