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:** Sep 23, 2019
**To:** "Jennifer E Dietrich" [redacted]
**From:** "The Green Journal" em@greenjournal.org
**Subject:** Your Submission ONG-19-1576

RE: Manuscript Number ONG-19-1576

Abnormal Uterine Bleeding in the Adolescent

Dear Dr. Dietrich:

Your manuscript has been reviewed by the Editorial Board and by special expert referees. Although it is judged not acceptable for publication in Obstetrics & Gynecology in its present form, we would be willing to give further consideration to a revised version.

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).

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 Oct 14, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

REVIEWER #1:

Drs. Hernandez and Dietrich present a very informative invited clinical expert review of abnormal uterine bleeding in the adolescent. All of the salient points regarding what makes caring for this diagnosis in this population are addressed. The flow of the paper is quite nice and easy to follow. I appreciate the effort to provide a concise education in this area for our providers who care for this population.

REVIEWER #2:

Abnormal Uterine Bleeding in the Adolescent in the Clinical Expert Series is a well-written, organized and concise article.

I found a sentences that could be improved/clarified:

1. Line 119 - I recommend the authors write out for what the acronym PBAC screening tool stands

2. Lines 176 and 177 Norethindrone acetate and norethindrone are redundant. Did the authors mean to use this medication name twice?

3. Line 229 What does 2082 represent? 2082 women? 2082 adolescents?

REVIEWER #3:

ONG-19-1576 Review

This review on abnormal uterine bleeding in the adolescent covers well known information, much of it summarized in ACOG Committee Opinions. Overall, the paper would benefit from improved organization, separating the studies on treatment options based on the underlying cause of abnormal bleeding, whether the patient is ovulatory or anovulatory, and whether the patient is presenting with acute, life-threatening hemorrhage or chronic abnormal uterine bleeding.

Abstract:

1. What is meant by "other warning signs that indicate a history of heavy bleeding?" This would be improved with

clarification.

Background:
2. "Abnormal cycles occur most frequently within the first 2-3 years after menarche:" Do the authors mean irregular cycles? As they next note, a degree of variability in menstrual cycle length is normal in the first several years after menarche.

Pathophysiology:

3. While a urine pregnancy test is certainly warranted, as well as a sexual history, the remainder of the evaluation should be determined by the details of the bleeding history. Every adolescent with heavy but cyclic menstrual bleeding does not need a pelvic exam, nor for PID to be ruled out.

4. In line 100, the authors note that up to 40% of girls with heavy menstrual bleeding may have an underlying bleeding disorder, while in line 119, they quote 20%

5. Line 136: Most guidelines on evaluating PCOS would not recommend all of the labs listed, as most are not relevant or necessary for the diagnosis (FSH/LH/E2, DHEAS)

6. Line 142: A serum prolactin level indicates hyperprolactinemia, which has a number of potential causes in addition to a prolactinoma. Not all patients with a prolactinoma will have visual changes, headaches, and galactorrhea.

Acute AUB:

7. The section on hormonal options would be strengthened by adding data on the efficacy of each of these options in the adolescent population.

8. The study discussing use of tranexamic acid referenced under Non-hormonal options refers to its use for chronic heavy menstrual bleeding. Are there any studies of tranexamic acid for acute vaginal bleeding in the adolescent?

9. Table 2: how long can IV tranexamic acid every 6-8 hours be continued?

10. Lines 222-7: The discussion of reference 26 is confusing, as it appears that a minority of the adolescents included had heavy menstrual bleeding, and discontinuation rates were high. As there are several meta-analyses reviewing these data, this study individually doesn't enhance the paper.

11. Lines 227-233: IS the comparison of levonorgestrel IUD to hysterectomy really relevant for adolescents? Hysterectomy presumably would be the very last choice, and only be considered in severe cases.

12. Table 3 is not referenced in the text, and there are no references provided for the data in it.

EDITORIAL OFFICE COMMENTS:

1. The Editors of Obstetrics & Gynecology are seeking to increase 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. As of December 17, 2018, Obstetrics & Gynecology has implemented an "electronic Copyright Transfer Agreement" (eCTA) and will no longer be collecting author agreement forms. When you are ready to revise your manuscript, you will be prompted in Editorial Manager (EM) to click on "Revise Submission." Doing so will launch the resubmission process, and you will be walked through the various questions that comprise the eCTA. Each of your coauthors will receive an email from the system requesting that they review and electronically sign the eCTA.

Please check with your coauthors to confirm that the disclosures listed in their eCTA forms are correctly disclosed 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 and gynecology data definitions at https://www.acog.org/About-ACOG/ACOG-Departments/Patient-Safety-and-Quality-Improvement/reVITALize. 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 not exceed 25 typed, double-spaced pages (6,250 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and print appendixes) 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).

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 limits for different article types are as follows: Clinical Expert Series, 300 words. Please provide a word count.

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.

8. 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.

9. 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.

10. 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 reference you are citing is still current and available. If the reference you are citing has been updated (ie, 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 (exceptions could include manuscripts that address items of historical interest). All ACOG documents (eg, Committee Opinions and Practice Bulletins) may be found via the Clinical Guidance & Publications page at https://www.acog.org/Clinical-Guidance-and-Publications/Search-Clinical-Guidance.

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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 in a word processing format such as Microsoft Word. 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.

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 Oct 14, 2019, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

The Editors of Obstetrics & Gynecology

2018 IMPACT FACTOR: 4.965
2018 IMPACT FACTOR RANKING: 7th out of 83 ob/gyn journals

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Dear Dr. Chesheir, Editor-In-Chief Obsetrics and Gynecology,

Thank you for your succinct review of our invited paper, “Abnormal Uterine bleeding in the adolescent” for the Clinical expert series. We have responded to reviewer comments and suggestions point by point below. We hope you will consider these changes adequate and look forward to your response.

Sincerely,

Jennifer E. Dietrich MD, MSc

REVIEWER #1:

Drs. Hernandez and Dietrich present a very informative invited clinical expert review of abnormal uterine bleeding in the adolescent. All of the salient points regarding what makes caring for this diagnosis in this population are addressed. The flow of the paper is quite nice and easy to follow. I appreciate the effort to provide a concise education in this area for our providers who care for this population.

Thank you for your comments.

REVIEWER #2:

Abnormal Uterine Bleeding in the Adolescent in the Clinical Expert Series is a well-written, organized and concise article.

I found a sentences that could be improved/clarified:

1. Line 119 - I recommend the authors write out for what the acronym PBAC screening tool stands
— We added the definition of PBAC

2. Lines 176 and 177 Norethindrone acetate and norethindrone are redundant. Did the authors mean to use this medication name twice?
—norethindrone (micronor) is different from norethindrone acetate (aygestin)
—in the table we don’t address a mircronor taper (since we usually only do that if the patient is on micronor already and calls with BTB. There are also limited studies comparing these two.

3. Line 229 What does 2082 represent? 2082 women? 2082 adolescents?
—we added women

REVIEWER #3:
separating the studies on treatment options based on the underlying cause of abnormal bleeding, whether the patient is ovulatory or anovulatory, and whether the patient is presenting with acute, life-threatening hemorrhage or chronic abnormal uterine bleeding.
—we do separate medical treatment into acute and chronic AUB
—ovulation status doesn't change the treatment, and we don't think separating studies would help address this.

Abstract:

1. What is meant by "other warning signs that indicate a history of heavy bleeding?" This would be improved with clarification.

- Thank you for this suggestion. We added in the word anemia.

Background:
2. "Abnormal cycles occur most frequently within the first 2-3 years after menarche:" Do the authors mean irregular cycles? As they next note, a degree of variability in menstrual cycle length is normal in the first several years after menarche.

- Thank you. The word "Abnormal" was changed to "irregular"

Pathophysiology:

3. While a urine pregnancy test is certainly warranted, as well as a sexual history, the remainder of the evaluation should be determined by the details of the bleeding history. Every adolescent with heavy but cyclic menstrual bleeding does not need a pelvic exam, nor for PID to be ruled out.
—reworded for clarity

4. In line 100, the authors note that up to 40% of girls with heavy menstrual bleeding may have an underlying bleeding disorder, while in line 119, they quote 20%
—this was in fact a typo, the facts I meant to have were 40% of adolescents complain of HMB and 20% of adolescents with HMB will have a bleeding disorder. Thank you for pointing this out.

5. Line 136: Most guidelines on evaluating PCOS would not recommend all of the labs listed, as most are not relevant or necessary for the diagnosis (FSH/LH/E2, DHEAS)
—changed to make the other labs a suggestion rather than part of the work-up, although many studies addressing adolescent PCOS require more stringent criteria for diagnosis and an adequate evaluation for oligomenorrhea and adrenal causes.

6. Line 142: A serum prolactin level indicates hyperprolactinemia, which has a number of potential causes in addition to a prolactinoma. Not all patients with a prolactinoma will have visual changes, headaches, and galactorrhea.
—changed for clarification

Acute AUB:

7. The section on hormonal options would be strengthened by adding data on the efficacy of each of these options in the adolescent population.
—addressed throughout the paper: Among those with a bleeding disorder, the levonogestrel IUD, followed by norethindrone acetate had the highest rates of success (89% and 83% respectively). Among those without a bleeding disorder, the transdermal patch and the levonogestrel IUD had the highest rates of success (100% and 80% respectively) [29].

8. The study discussing use of tranexamic acid referenced under Non-hormonal options refers to its use for chronic heavy menstrual bleeding. Are there any studies of tranexamic acid for acute vaginal bleeding in the adolescent?
—There are no specific studies to date that isolate acute HMB from chronic HMB and the use of TXA. This is a newer medication and has been used quite a bit in trauma, cardiac surgery and post-partum hemorrhage. All studies to date include TXA as an option for management of both acute and chronic bleeding.

9. Table 2: how long can IV tranexamic acid every 6-8 hours be continued?
—added until bleeding subsides. As suggested by the reference included, treatment duration is usually tailored according to clinical bleeding and may be stopped without tapering when heavy menstrual bleeding subsides.

10. Lines 222-7: The discussion of reference 26 is confusing, as it appears that a minority of the adolescents included had heavy menstrual bleeding, and discontinuation rates were high. As there are several meta-analyses reviewing these data, this study individually doesn't enhance the paper.
—highlighted this study discussion
—We agree this is not a strong level of evidence, however, it is one of the few papers addressing use of norethindrone acetate use in this population, which is why we included it. It is also relevant to point out the attrition rate as there is a high rate of attrition from therapies in adolescents in general so this models real world.

11. Lines 227-233: IS the comparison of levonorgestrel IUD to hysterectomy really relevant for adolescents? Hysterectomy presumably would be the very last choice, and only be considered in severe cases.
—This is a study that we are quoting, however, we tried to reemphasize that hysterectomy is a last resort in this population.

12. Table 3 is not referenced in the text, and there are no references provided for the data in it.
—We added norethindrone acetate to the table (5-15mg daily) since we discuss it in the text. I cited the table in the first sentence of the section. There is a reference [6] for the table next to its title.