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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)*
- Email correspondence between the editorial office and the authors*

*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.
RE: Manuscript Number ONG-19-33

Approaches to vaginal bleeding and contraceptive counseling in transgender patients

Dear Dr. Schwartz:

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 Feb 28, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: This is a well-written and comprehensive review of "Approaches to vaginal bleeding and contraceptive counseling" in transgender patients.

1. As currently written, the review represents a comprehensive review of office gynecologic care far in excess of the narrow title; will suggest a broader title, for example; "Office gynecologic care of transgender patients". If authors wish to retain the original title, the abstract (lines 47-56) needs to be heavily edited for brevity. Further, (in the narrower context), defining transgender population (72-104) so extensively would seem unnecessary as is the transgender prevalence section (106-115). The latter can be solely focused on the prevalence of abnormal uterine bleeding in the transgender population. However, none of this will be necessary if the title is edited as suggested.

2. Although the article title and much of discussions reference transgender and transmen, how about transwomen? - if the latter is not within the scope of this review, it should be stated as such early in the review. Even so, a brief synopsis of issues these individuals encounter will be quite useful.

3. In describing etiological factors for abnormal uterine bleeding throughout the manuscript, authors may wish to use the FIGO categorization of AUB, namely PALMCOEIN*.

4. The discussions very appropriately identified provider education issues as a barrier to healthcare; how about ancillary staff?- nurses (in the office setting, in-patients), desk staff, clinic assistants, ultrasonographers (especially in the setting of infertility treatments that require frequent encounters) must be equally ignorant of the needs of this group of patients. Therefore, improving access to care and the quality of care must include plans to address these diverse groups of healthcare providers and support staff. Please consider including a discussion on this.

5. Authors may wish to re-arrange the manuscript by starting the discussions on adolescent or young adult issues (menstrual suppression- 283-402) prior to AUB discussions (218-), then fertility issues & contraception.

6. Some additional clarifications; Lines 135-137; what specifically are authors recommending? Lines 246-251; what is the take-home message on the effect of testosterone on the uterus? Line 276; substitute "is no lower" with "equivalent" Lines 283-300, how long should GnRH be used? Any recommendations for add-back therapy, if so, what agent? Please replace line 305 "in- talking.." with less colloquial words. Lines 316, what contraindications?

7. Are there additional long -term risks (epigenetics) of testosterone exposure of female fetus, such as risks of developing polycystic ovaries syndrome or metabolic syndrome in adulthood?
8. Consider creating a table of gender-affirming drugs (GnRH, T, Letrozole etc), specifying typical dosing & side effects? Readers may find it practical and useful.


Reviewer #2: Dr. Schwartz and colleagues have submitted a meaningful review of current literature and recommendations for evaluation and management of vaginal bleeding and contraceptive management for transgender and gender non-conforming patients. The subject matter is very important, given the paucity of publications guiding management of this unique and important patient population as well as the fact that many in this patient population present to community health centers. A comprehensive review of this issue in mainstream OB/GYN literature would be extremely valuable. With some minor edits for clarity, flow, and assurance of the quality of guiding data, this manuscript will represent an important contribution to the literature. Overall, increasing clarity of methods of data review and assuring focus on the question at hand (vaginal bleeding and contraception management) will improve the manuscript.

Abstract: No comments

Transgender population: This is a great summary of the accepted terminology as well as definitions and diagnoses, which are important for coding and determining the appropriate care

Prevalence: I would suggest keeping the overall message of this segment focused on the difficulty of measuring the prevalence because of variable definitions, stigma, and the overall social construct of gender influencing reporting. Citing the Van Kesteren study as an early estimate seems unnecessary (line 108-110). This study was limited to the Netherlands at one time point, so I don’t think it can serve as a comparison to more recent estimates from the US and other countries. I might stick to presenting the Winter study. However, calling this a sampling of the general population is not totally accurate (line 110). This is a summary of other studies where populations were estimated from various countries. The Gates citation is no longer available (Lines 113-115). The only Gallup poll I could find with similar data reported simply on LGBT as a whole as a growing population, not specifically transgender community. This should be clarified.

Diagnosis and Management:
Line 120: Add a citation to each of the reports from WPATH and the Endocrine Society

Health care barriers and unique needs:
Line 150: The Shields study doesn’t present data that supports this statement. I might search for the citation within this paper that might have data that better supports that statement. Otherwise, remove the statement.

Lines 156-162: I would reference the Transgender Law Center data for some of these statements, and might see if citation #10 (Injustice at every turn..) also presents some data that supports these statements.

Lines 193-205: I would reference resources from WPATH as well as UCSF’s Center of Excellence in Transgender care for some of these recommendations regarding measures taken to keep patient comfortable in the clinical setting/exam room.

Approach to vaginal bleeding:
Line 233-4: Consider word choice change: "Abnormal uterine bleeding in a transgender man with a uterus requires workup similar to cisgender women to evaluate for endometrial sources of bleeding or endometrial malignancies."

Lines 236-238: The statement that exogenous testosterone can aromatize to estrogen and cause a theoretical increased risk of endometrial hyperplasia and carcinoma should be clarified. This statement is based on very limited data. It might be better presented as a historical consideration, explaining previous recommendations to use testosterone for limited time before gender affirming hysterectomy with decreased dose postop. I might reframe the paragraph here to present this study as a consideration previously, then clarify in line 238 that the case report by Urban et al supports the theory of hypoestrogenic state with inhibition of endometrial cell growth. Then go into the more recent studies that are more mixed. However, please clarify where the data leans more strongly and make sure to clarify if there are any recommendations for limitations on testosterone therapy based on the endometrial hyperplasia concern.

Lines 242-246: Clarify that this is a study of 112 pathologic specimens. Please also compare to rates of hyperplasia/adenocarcinoma in the general population, and if there was any clarifying information regarding other risk factors, particularly for those specimens with hyperplasia/adenocarcinoma. Given the increasing prevalence of risk factors for these disease processes, it is important to understand if this is something unique to this patient population versus and overall population trend.
Lines 246-249: Again, clarify that the N of this study, which was 27.

Lines 249-251: Again, this is very limited data. Ref 29 includes only 12 cases, and Ref 30 is a dissertation that doesn't seem very available to the public. Is there a corresponding manuscript?

Line 253: Consider word choice change: "Transgender men with vaginal bleeding should be assessed for other gynecologic sources of bleeding (on the basis of their present anatomy) and screened for sexually transmitted infections (STIs).

Lines 255-259: I would consider reversing the order of these sentences.

Lines 266-268: It seems that the data regarding unsatisfactory pap smear specimens in this study was amongst all-comers, not just transgender patients, and this may not be a patient population that is generalizable specifically to the transgender population. Please clarify if this is a trend for all-comers, or if there is data to support this concern specifically for transgender populations.

Lines 279-275: Please state the sensitivity and specificity of physician-collected samples to clarify the acceptable differences.

Lines 277-279: Please reference a source with more specific numbers on sensitivity and specificity of self-swabs for GC/Chlamydia.

Menstrual Suppression: Overall this is a very valuable segment and clearly an important component of the paper overall. However, the text seems to shift between considering menstrual suppression and pubertal suppression or suppression of secondary sex characteristics. Please review the segment overall and separate recommendations for therapy for menstrual suppression and for suppression of secondary sex characteristics. Additionally, if you are going to include both in this segment, consider renaming the segment including something about pubertal suppression. Otherwise, you may want to separate them completely and place all the information about suppression of secondary sex characteristics into a separate section.

Lines 294-298: the wording of this sentence is confusing, specifically "Suppression of puberty with GnRH agonists is advantageous by both reversibility preventing development of unwanted secondary sex characteristics and providing time for continued gender identity..." Please re-word.

Lines 305-313: While this paragraph is important for overall considerations, it doesn't seem to flow in this place in the paper. I might move this to the health care barriers and unique needs segment.

Line 316: You reference contraindications, but these were not listed anywhere. Please list these earlier in the discussion of GnRH agonist pubertal suppression.

Lines 396-398: I prefer in if discussion of surgical management starts with less invasive options and moves towards more invasive options. I would suggest moving discussion of endometrial ablation to before hysterectomy discussion. This will also allow for more intuitive transition for considerations at the time of hysterectomy such as bilateral oophorectomy.

Line 402: Please clarify the risks of premenopausal oophorectomy in the general population and why this may differ in the setting of long term testosterone therapy (bone density considerations, cardiovascular risks, etc).

Fertility options for transgender men: No comments

Testosterone and reproduction:
Line 441-442: Consider deleting "or ovarian cysts"

Lines 446-452: you make a transition from talking about the effects of testosterone on ovarian function to contraception, but it is not a clear transition. Since there is a segment specifically on contraception, I would remove statements about contraception and stick to stating the unreliable suppression of ovarian function by testosterone and the contraindications to pregnancy with exogenous testosterone.

Contraceptive Selection:
Lines 462-463: You quote a 32% rate of unintended pregnancies, which is actually better than the overall rate of 47% of pregnancies being unintended. It doesn't clarify the importance of the problem. Maybe compare it to unintended pregnancy rates in other patient populations on medications that are contraindications to pregnancy, such as those on tretinoin etc.

Lines 464-465: Once again, how do these compare to the general population, and if comparable, why is this important (ie why is it more important for this patient population to have more reliable contraception)?

Line 467: replace Efficacy with Effectiveness

Line 487: replace activating with acting
Avoid reference to a brand name, given the data supporting comparability of Liletta and Mirena. There are also more recent data for Liletta for menstrual suppression. Provide data supporting use of both and talk more generally about the 52mg Levonorgestrel IUD. Some institutions will only have Liletta available or only Mirena, and it is important that they can be used interchangeably.

I would reference the ACOG Practice Bulletin on Emergency Contraception.

References:

is there a follow up publication for this reference? It seems this is a pilot study, and I’m wondering if there is more definitive data published since 2007.

I might also reference the latest edition of the Hatcher text, Contraceptive Technology for this general information and the table on contraceptive options.

Table 1: Overall, this is a great inclusion for the manuscript, and very good for practical use.

Progesterone-only contraceptive pills Mechanism: Do you want to list primary and secondary mechanisms and clarify that? I think just listing ovulation suppression is misleading, because this is not a reliable mechanism for these, as it only takes place about 50% of the time. Advantages: with regard to androgenic progestins, this is not very applicable in the US, where POPs only come in one form.

NuvaRing Disadvantages: You should list thrombotic risk here as well

You are missing contraceptive patch option

Medroxyprogesterone acetate injection Disadvantages: I would not use the word osteoporosis, because that is a specific diagnosis. What is observed is reversible decreased bone mineral density.

Bilateral tubal ligation: Consider adding to title "permanent contraception." Under disadvantages, I would leave it at impossible to reverse, because reversal is not recommended by most REIs, and very few in the country will perform reversals. This should not be considered in anybody who may want pregnancy in the future.

Copper IUD: I would separate discussion of Cu IUD for contraception and for emergency contraception. It is confusing that it is only listed under emergency contraception, but then described as both. With regard to emergency contraception mechanism of action, you may want to disclose that this is the only EC option that may prevent implantation of a fertilized egg.

Progesterone pill for EC: Clarify that it can be used up to 120 hours post unprotected intercourse, but effectiveness decreases after 72 hours.

Figure 1: No comments.

I thank the authors for their paper on an important topic for women's health care providers. While I agree that most primary care providers are not experienced to provide optimal care to the transgender community, this submitted paper is confusing in that it fails to focus on the subject matter communicated by the title of the paper. Accordingly, the authors should consider to pen a systematic review of gynecologic care for transgender individuals or to focus a paper on the title that is found on this submission. The attempt by the authors to provide a comprehensive overview has rendered this paper poorly focused and difficult to follow.

Although this is very well-written, I do not think this adds a significant amount to existing literature.

1. Your paper has terrific content. However, I have to agree with Reviewer 3's comments. Your title suggests that you will be writing about the transman or gender non conforming person with female natal sex who has unexpected vaginal
bleeding. While you manuscript includes this information, you also include a great deal of medical, epidemiologic and primary care information such that your paper is unfocused. If you wanted to provide a general guide for the OB GYN (the readers of this journal) for caring for transmen and gender non conforming people with natal female sex anatomy, then you have much more to consider including (mammography? breast binding hows? pregnancy and lactation? violence screening/ PREP?). If you really wanted to focus on vaginal bleeding, you have way too much general information about this population. You really need to decide and then revise your paper--title, abstract, and paper--accordingly.

2. In addition to the comments from the reviewers above, you are being sent a notated PDF that contains the Editor’s specific comments. Please review and consider the comments in this file prior to submitting your revised manuscript.

***The notated PDF is uploaded to this submission's record in Editorial Manager. If you cannot locate the file, contact Randi Zung and she will send it by email - rzung@greenjournal.org.***

- Although this is not a systematic review and the exact description of the contents of the abstract won't apply, it should still be focused and <= 300 words. As noted by at least one of your reviewers, your article has a lot of general information about transgender health, while your title suggests this paper is about the evaluation of transgender people (it might be useful to say transmen since transwomen don't have uterusus and it would help the readers get used to what for some is unfamiliar terminology. If you revise your paper to report on the evaluation of transmen with unexpected vaginal bleeding, then your abstract should focus on that.

- warrants measurement of hormone levels

- can be used

- The Journal style doesn’t use the virgule (/) except in numeric expressions. Please edit here and in all instances.

- transpeople who have gender affirming surgeries still require hormonal therapy. Shoud this be an "or" or an "And"

- We had a terrific grand rounds at UNC on transmen and pregnancy today and it was the first time I had ever heard of "tucking". It makes sense, I had just never heard the word before. It may be useful to define this a bit more. It was used in the full description of "tucking and taping".

- appropriate here to ask for what terms transmen use for their anatomy related to the sex? (not gender)

- while on continuous testosterone therapy

- work-up is jargon. Consider "evaluation" or "diagnostic evaluation".

- other than testosterone, are their other gender-affirming hormonal therapies? could you be clear about what hormones you mean rather than using their indication only (gender affirming) please state the types.

- On the other hand, androgens have been shown....

- for clarity, would you consider ...have shown upregulation of neither Ki-67....nor ZIC2.

- from here to end of paragraph you are not really addressing vaginal bleeding but general health issues.

- again, if you mean all trans people, fine to use transgender here, but it seems you specifically mean transmen. If you could be clear about the terminology and use the specific term when you mean it specifically, that would be helpful

- this patient pop--is that HIV positive or transmen? Please clarify

- if an negative result is obtained on self collected specimen do you recommend a provider obtained specimen?

- Not sure what this means. Other than frank hemorrhage, isn't most endometrial bleeding breakthrough bleeding from capillaries?

- by my count, this is at least the 3rd time you've mentioned this. Please condense.

- is it not acceptable for transmen testosterone?

3. 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, as well as subsequent author queries. 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:

1. OPT-IN: Yes, please publish my response letter and subsequent email correspondence related to author queries.
2. OPT-OUT: No, please do not publish my response letter and subsequent email correspondence related to author queries.

4. 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.

Any author agreement forms previously submitted will be superseded by the eCTA. During the resubmission process, you are welcome to remove these PDFs from EM. However, if you prefer, we can remove them for you after submission.

5. Figure 1: Should be a text box instead of a figure. Author also needs to obtain permission to use this source.

Tables, figures, and supplemental digital content should be original. The use of borrowed material (eg, lengthy direct quotations, tables, figures, or videos) is discouraged, but should it be considered essential, written permission of the copyright holder must be obtained. Permission is also required for material that has been adapted or modified from another source. Both print and electronic (online) rights must be obtained from the holder of the copyright (often the publisher, not the author), and credit to the original source must be included in your manuscript. Many publishers now have online systems for submitting permissions request; please consult the publisher directly for more information.

6. 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.

7. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Review 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 appendices) but exclude references.

8. 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).

9. 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: Reviews, 300 words. Please provide a word count.

10. 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.

11. The commercial name (with the generic name in parentheses) may be used once in the body of the manuscript. Use the generic name at each mention thereafter. Commercial names should not be used in the title, précis, or abstract.

12. 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.
13. 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.

14. 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.

15. Authors whose manuscripts have been accepted for publication have the option to pay an article processing charge and publish open access. With this choice, articles are made freely available online immediately upon publication. An information sheet is available at http://links.lww.com/LWW-ES/A48. The cost for publishing an article as open access can be found at http://edmgr.ovid.com/acd/accounts/ifauth.htm.

Please note that if your article is accepted, you will receive an email from the editorial office asking you to choose a publication route (traditional or open access). Please keep an eye out for that future email and be sure to respond to it promptly.

16. If you choose to revise your manuscript, please submit your revision via Editorial Manager for Obstetrics & Gynecology at http://ong.editorialmanager.com. It is essential that your cover letter list point-by-point the changes made in response to each criticism. Also, please save and submit your manuscript in a word processing format such as Microsoft Word.

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 Feb 28, 2019, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,
Nancy C. Chescheir, MD
Editor-in-Chief

2017 IMPACT FACTOR: 4.982
2017 IMPACT FACTOR RANKING: 5th out of 82 ob/gyn journals

In compliance with data protection regulations, please contact the publication office if you would like to have your personal information removed from the database.
Dear Dr. Chescheir:

We wish to submit our revised original research article entitled “Office gynecologic care of transgender and non-binary patients: managing vaginal bleeding and contraception” for consideration for publication in Obstetrics and Gynecology. In this review article we aim to address the gap in knowledge of gynecologic and contraceptive care for transgender and gender non-binary individuals. This article discusses the history of discrimination and disparities in healthcare of the transgender population as well as recommendations for diagnosis and treatment of gender dysphoria. In the discussion of vaginal bleeding, we review methods of pubertal suppression, the mechanism of testosterone-induced amenorrhea and recommendations for treatment of breakthrough bleeding in this patient population. Fertility options and the importance of reproductive counseling for transgender patients is addressed. Finally, we discuss contraceptive counseling for transgender adolescents and adults with emphasis on advantages and disadvantages of birth control options as it relates to the gender identity of these patients. We are very much appreciative of your time and consideration.

We submit this revised review solely to Obstetrics and Gynecology. This manuscript is not under consideration elsewhere and will not be submitted elsewhere until a final decision is made by the Editors of Obstetrics and Gynecology. The lead author, Amanda Rae Schwartz, affirms that this manuscript is an honest, accurate and transparent account of the review study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained. We have included in this cover letter our point-by-point responses to reviewer critiques.

Signed by: Amanda Rae Schwartz

As this is a review article, no IRB approval was necessary. We have no conflicts of interest to disclose.

Sincerely,

Amanda Rae Schwartz, MD
Obstetrics and Gynecology Resident
Reviewer #1: This is a well-written and comprehensive review of "Approaches to vaginal bleeding and contraceptive counseling" in transgender patients.

1. As currently written, the review represents a comprehensive review of office gynecologic care far in excess of the narrow title; will suggest a broader title, for example; "Office gynecologic care of transgender patients". If authors wish to retain the original title, the abstract (lines 47-56) needs to be heavily edited for brevity. Further, (in the narrower context), defining transgender population (72-104) so extensively would seem unnecessary as is the transgender prevalence section (106-115). The latter can be solely focused on the prevalence of abnormal uterine bleeding in the transgender population. However, none of this will be necessary if the title is edited as suggested.

Response: We agree that the title needs to be reframed given the broader coverage in the context of the review. Therefore the review was retitled: Office gynecologic care of transgender and gender non-binary patients: managing vaginal bleeding and contraception.

2. Although the article title and much of discussions reference transgender and transmen, how about transwomen? - if the latter is not within the scope of this review, it should be stated as such early in the review. Even so, a brief synopsis of issues these individuals encounter will be quite useful.

Response: We believe that care of transwomen is outside the scope of this review. Lines 122 - 125: "Transgender men and gender non-conforming individuals commonly present to a gynecologist for ambulatory care, while transwomen are much less likely to do so. Therefore, this review will focus on gynecologic care for transgender men and gender non-conforming patients with natal female anatomy."

3. In describing etiological factors for abnormal uterine bleeding throughout the manuscript, authors may wish to use the FIGO categorization of AUB, namely PALMCOEIN*.

Response: We agree with the reviewer that the FIGO categorization of abnormal uterine bleeding more clearly describes etiologies of bleeding to be considered in the described patient population. Therefore, citation #22 was added to the list of references. Lines 330 - 334: "In the differential diagnosis one should consider pregnancy in sexually active transgender men who have sex with men as well as etiologies of abnormal uterine bleeding depicted in the PALM-COEIN classification system including polyps, adenomyosis, leiomyomas, malignancy and hyperplasia, coagulation defects, ovulatory dysfunction, endometrial abnormalities and iatrogenic causes."

4. The discussions very appropriately identified provider education issues as a barrier to healthcare; how about ancillary staff? - nurses (in the office setting, in-patients), desk staff, clinic assistants, ultrasonographers (especially in the setting of infertility treatments that require frequent encounters) must be equally ignorant of the needs of this group of patients. Therefore, improving access to care and the quality of care must include plans to address these diverse groups of healthcare providers and support staff. Please consider including a discussion on this.

Response: We agree with the reviewer that clinic changes should be broadened to include all participants in the patient’s care in order to create a truly inclusive environment. This changes in reflected in the edited manuscript in lines 298 – 301: "The creation of a welcoming environment for transgender and
gender non-conforming individuals must reach beyond the level of the physician. Training on transgender healthcare barriers and inclusion should extend to front desk staff, clinic assistants, nurses and ultrasonographers so that patients are affirmed throughout the entirety of their clinic visit.

5. Authors may wish to re-arrange the manuscript by starting the discussions on adolescent or young adult issues (menstrual suppression- 283-402) prior to AUB discussions (218-), then fertility issues & contraception.

Response: While we appreciate the reviewer’s suggestion, we prefer the order as listed.

6. Some additional clarifications; Lines 135-137; what specifically are authors recommending? Lines 246-251; what is the take-home message on the effect of testosterone on the uterus? Line 276; substitute "is no lower" with "equivalent" Lines 283-300, how long should GnRH be used? Any recommendations for add-back therapy, if so, what agent? Please replace line 305 "in- talking.." with less colloquial words. Lines 316, what contraindications?

Response: Lines 192 - 194: “Some patients may seek to initiate gender affirming hormones prior to, or in concert with their social transition, so that they may better assimilate and be seen and interacted with according to their gender identity.” We feel that this decision should be up to the patient and the process by which they wish to affirm their identity.

Response: We agree with the reviewer that the take-home message on the effect of testosterone on the uterus requires clarification. This changes is reflected in the manuscript in lines 341 – 346: Historically it was recommended to prescribe testosterone for a limited time prior to gender-affirming surgery due to the theoretical concern that exogenous testosterone can aromatize to estrogen with an increased risk of endometrial hyperplasia and carcinoma. However, more recent data supports the theory that androgens induce a hypoestrogenic state with inhibition of endometrial cell growth and secretor activity and subsequent endometrial atrophy with decreased risk of malignant progression” as well as lines 374 – 376: “These results provide further evidence for an inhibitory rather than stimulatory effect of testosterone on endometrial cell growth.”

Response: We agree with the reviewer that this statement requires clarification. This change is reflected in the manuscript in lines 416 - 418: “A meta-analysis of the sexual behavior of transgender men concluded that the risk of STIs among transgender men is comparable to cisgender women and routine screening should be offered.”

Response: We agree with the reviewer that more information on GnRH agonist dosing would be useful in the manuscript. This change is reflected in lines 458 - 462: “Although there is no consensus on the duration of GnRH agonist therapy, GnRH agonists should not be used alone indefinitely as bone mineralization requires the presence of sex steroids. GnRH agonists may be continued in tandem with gender-affirming hormones into late adolescence or early adults hood as continued suppression of the hypothalamic-pituitary-gonadal axis may permit lower hormone dosing.”

Response: We agree with the reviewer that these phrasing was colloquial, this revision is reflected in lines: Lines 109 - 122: “Avoiding the assumption that patients assigned female at birth and identifying as transgender are transgender men or that patients assigned male at birth who identify as transgender are automatically transgender women, illustrates the provider’s knowledge about the diversity within the gender continuum.”

Response: We agree with the reviewer that these contraindications should be discussed. This changes is reflected in the manuscript in lines: “Lines 464 – 466: “Progestin therapy may be considered as an
alternative to GnRH agonists for pubertal suppression in patients with medical contraindications to first line therapy, including known hypersensitivity to GnRH agonists, pregnancy and lactation, or who present at later pubertal stages.

7. Are there additional long-term risks (epigenetics) of testosterone exposure of female fetus, such as risks of developing polycystic ovaries syndrome or metabolic syndrome in adulthood?

Response: none found

8. Consider creating a table of gender-affirming drugs (GnRH, T, Letrozole etc.), specifying typical dosing & side effects? Readers may find it practical and useful.

Response: We agree with both the reviewer and the Editor in Chief that a table of gender-affirming hormone therapy would be practical and useful. Given that the focus of this review is on transgender men and gender non-conforming individuals the table includes testosterone preparations and dosing regimens. This information is presented in the revised manuscript in Table 1.

Reviewer #2: Dr. Schwartz and colleagues have submitted a meaningful review of current literature and recommendations for evaluation and management of vaginal bleeding and contraceptive management for transgender and gender non-conforming patients. The subject matter is very important, given the paucity of publications guiding management of this unique and important patient population as well as the fact that many in this patient population present to community health centers. A comprehensive review of this issue in mainstream OB/GYN literature would be extremely valuable. With some minor edits for clarity, flow, and assurance of the quality of guiding data, this manuscript will represent an important contribution to the literature. Overall, increasing clarity of methods of data review and assuring focus on the question at hand (vaginal bleeding and contraception management) will improve the manuscript.

Abstract: No comments

Transgender population: This is a great summary of the accepted terminology as well as definitions and diagnoses, which are important for coding and determining the appropriate care

Prevalence: I would suggest keeping the overall message of this segment focused on the difficulty of measuring the prevalence because of variable definitions, stigma, and the overall social construct of gender influencing reporting. Citing the Van Kesteren study as an early estimate seems unnecessary (line 108-110). This study was limited to the Netherlands at one time point, so I don't think it can serve as a comparison to more recent estimates from the US and other countries. I might stick to presenting the Winter study. However, calling this a sampling of the general population is not totally accurate (line 110). This is a summary of other studies where populations were estimated from various countries. The Gates citation is no longer available (Lines 113-115). The only Gallup poll I could find with similar data reported simply on LGBT as a whole as a growing population, not specifically transgender community. This should be clarified.

Response: We agree with the reviewer’s points discussed in the section on prevalence. The Gallup citation was removed. The Van Kesteren study was likewise removed given that it reflected only the Netherlands data at a single point in time.

Diagnosis and Management:

Line 120: Add a citation to each of the reports from WPATH and the Endocrine Society
Response: The citations requested from the reviewer were added. This change is reflected in line 163 of the revised manuscript.

Health care barriers and unique needs:
Line 150: The Shields study doesn't present data that supports this statement. I might search for the citation within this paper that might have data that better supports that statement. Otherwise, remove the statement.

Response: The Shields study was removed from the revised manuscript.

Lines 156-162: I would reference the Transgender Law Center data for some of these statements, and might see if citation #10 (Injustice at every turn..) also presents some data that supports these statements.

Response: We agree with the reviewer that referencing Transgender Law Center data is useful in this section of the manuscript. This is reflected in the addition of citation #11 in lines 233 – 234: “This fear is not misplaced as transgender patients are more likely than their cisgender peers to experience healthcare discrimination”.

Lines 193-205: I would reference resources from WPATH as well as UCSF’s Center of Excellence in Transgender care for some of these recommendations regarding measures taken to keep patient comfortable in the clinical setting/exam room.

Response: We agree with the reviewer that referencing these resources would be useful for this discussion. The changes are reflected in lines 299 – 301: “Training on transgender healthcare barriers and inclusion should extend to front desk staff, clinic assistants, nurses and ultrasonographers so that patients are affirmed throughout the entirety of their clinic visit” and lines 304 - 306: “Having gender neutral bathrooms and developing policies against gender discrimination can create an environment that is both welcoming and affirming for transgender and non-binary patients.”

Approach to vaginal bleeding:
Line 233-4: Consider word choice change: "Abnormal uterine bleeding in a transgender man with a uterus requires workup similar to cisgender women to evaluate for endometrial sources of bleeding or endometrial malignancies."

Response: We agree with the reviewer that this statement as previously written is confusing. It has been revised with the change reflected in lines 336 – 337: “Abnormal uterine bleeding in a transgender man with a uterus requires an evaluation similar to cisgender women to evaluate for endometrial malignancy.”

Lines 236-238: The statement that exogenous testosterone can aromatize to estrogen and cause a theoretical increased risk of endometrial hyperplasia and carcinoma should be clarified. This statement is based on very limited data. It might be better presented as a historical consideration, explaining previous recommendations to use testosterone for limited time before gender affirming hysterectomy with decreased dose postop. I might reframe the paragraph here to present this study as a consideration previously, then clarify in line 238 that the case report by Urban et al supports the theory of hypoestrogenic state with inhibition of endometrial cell growth. Then go into the more recent studies that are more mixed. However, please clarify where the data leans more strongly and make sure to clarify if there are any recommendations for limitations on testosterone therapy based on the endometrial hyperplasia concern.
Response: We agree with the reviewer that the take-home message on the effect of testosterone on the uterus requires clarification. This change is reflected in the manuscript in lines 341 – 346: Historically it was recommended to prescribe testosterone for a limited time prior to gender-affirming surgery due to the theoretical concern that exogenous testosterone can aromatize to estrogen with an increased risk of endometrial hyperplasia and carcinoma. However, more recent data supports the theory that androgens induce a hypoestrogenic state with inhibition of endometrial cell growth and secretor activity and subsequent endometrial atrophy with decreased risk of malignant progression” as well as lines 374 – 376: “These results provide further evidence for an inhibitory rather than stimulatory effect of testosterone on endometrial cell growth.”

Lines 242-246: Clarify that this is a study of 112 pathologic specimens. Please also compare to rates of hyperplasia/adenocarcinoma in the general population, and if there was any clarifying information regarding other risk factors, particularly for those specimens with hyperplasia/adenocarcinoma. Given the increasing prevalence of risk factors for these disease processes, it is important to understand if this is something unique to this patient population versus and overall population trend.

Response: We agree with the reviewer that the sample size of these studies should be stated in the manuscript. This change is reflected in lines 348 – 372: “An analysis of 112 hysterectomy tissue samples after prolonged testosterone therapy showed mixed results with proliferative endometrium in 48% of patients, endometrial atrophy in 45%, endometrial hyperplasia without atypia in eight patients and a single case of focal endometrial adenocarcinoma. In this study there was no correlation with age or body mass index on endometrial histology. In contrast, another analysis of 27 post-hysterectomy samples, revealed inactive endometrium in all subjects with endometrial atrophy similar to postmenopausal women, thus concluding that testosterone therapy does not increase risk of endometrial stimulation in transgender men.”

Lines 249-251: Again, this is very limited data. Ref 29 includes only 12 cases, and Ref 30 is a dissertation that doesn't seem very available to the public. Is there a corresponding manuscript?

Response: We appreciate the reviewers concerns. We are unable to find a corresponding manuscript, though the dissertation is available to the public at: https://hdl.handle.net/2144/23727

Line 253: Consider word choice change: "Transgender men with vaginal bleeding should be assessed for other gynecologic sources of bleeding (on the basis of their present anatomy) and screened for sexually transmitted infections (STIs).

Response: We agree with the reviewer that this sentence should be revised. This changes is reflected in lines 378 – 379: “Transgender men with vaginal bleeding should be assessed for other gynecologic sources of bleeding and screened for sexually transmitted infections (STIs).

Lines 255-259: I would consider reversing the order of these sentences.

Response: We agree with the reviewer and therefore the order of the statements was reversed.

Lines 266-268: It seems that the data regarding unsatisfactory pap smear specimens in this study was amongst all-comers, not just transgender patients, and this may not be a patient population that is generalizable specifically to the transgender population. Please clarify if this is a trend for all-comers, or if there is data to support this concern specifically for transgender populations.

Response: We appreciate the reviewers concerns. These studies were of unsatisfactory pap smears in women and were not just transgender patients. This is reflected in the manuscript in lines 405 – 406:
“While testosterone-induced atrophy may contribute to unsatisfactory findings, individuals with a history of an unsatisfactory pap smear are at increased risk of cervical dysplasia.”

Lines 273-275: Please state the sensitivity and specificity of physician-collected samples to clarify the acceptable differences.

Response: We agree with the reviewer that the requested information would clarify the differences. This change is reflected in lines 410 – 413: “In a study of 150 transmen with a cervix, a self-collected HPV swab had a sensitivity of 71% and specificity of 98% as compared to the gold standard of a physician-collected cervical HPV swab. Over 90% of the study participants endorsed a preference for the self-collected sample.”

Lines 277-279: Please reference a source with more specific numbers on sensitivity and specificity of self-swabs for GC/Chlamydia.

Response: We agree with the reviewer that statistics of self-swabs for gonorrhea and chlamydia would be useful to readers. This change is reflected in lines 418 – 421: “The high specificity and sensitivity of self-collected vaginal swabs for gonorrhea (98% sensitivity, 97% specificity) and chlamydia (92% sensitivity, 98% specificity) should motivate providers to discuss the option of self-testing with their transgender patients and is another example of providers making efforts to minimize discomfort.”

Menstrual Suppression: Overall this is a very valuable segment and clearly an important component of the paper overall. However, the text seems to shift between considering menstrual suppression and pubertal suppression or suppression of secondary sex characteristics. Please review the segment overall and separate recommendations for therapy for menstrual suppression and for suppression of secondary sex characteristics. Additionally, if you are going to include both in this segment, consider renaming the segment including something about pubertal suppression. Otherwise, you may want to separate them completely and place all the information about suppression of secondary sex characteristics into a separate section.

Response: We agree with the reviewer that this section could be separated into separate headings for pubertal suppression and menstrual suppression to allow more direction for the reader. This change is reflected in re-naming the earlier section “Pubertal Suppression”

Lines 294-298: the wording of this sentence is confusing, specifically "Suppression of puberty wit GnRH agonists is advantageous by both reversibility preventing development of unwanted secondary sex characteristics and providing time for continued gender identity…” Please re-word.

Response: We agree with the reviewer that this statement should be edited. This changes is reflected in lines 452 – 454: “As a reversible treatment, GnRH agonists provide time for continued gender identity development and for multidisciplinary teams to confirm diagnosis and formulate appropriate treatment plans should gender dysphoria persist.”

Lines 305-313: While this paragraph is important for overall considerations, it doesn't seem to flow in this place in the paper. I might move this to the health care barriers and unique needs segment.

Response: We agree with the reviewer. This discussion was moved to the discussion of the transgender population.

Line 316: You reference contraindications, but these were not listed anywhere. Please list these earlier in the discussion of GnRH agonist pubertal suppression.
Response: Lines 464 – 466: Progestin therapy may be considered as an alternative to GnRH agonists for pubertal suppression in patients who have medical contraindications to first line therapy, including known hypersensitivity to GnRH agonists, pregnancy or lactation, or who present at later pubertal stages.

Lines 396-398: I prefer if discussion of surgical management starts with less invasive options and moves towards more invasive options. I would suggest moving discussion of endometrial ablation to before hysterectomy discussion. This will also allow for more intuitive transition for considerations at the time of hysterectomy such as bilateral oophorectomy.

Response: We agree with the reviewer that discussion of the less invasive endometrial ablation should precede discussion of surgical approach for hysterectomy. The manuscript was revised to reflect this change.

Line 402: Please clarify the risks of premenopausal oophorectomy in the general population and why this may differ in the setting of long term testosterone therapy (bone density considerations, cardiovascular risks, etc).

Response: We agree with the reviewer that discussion of risks of premenopausal oophorectomy should be included in the review. This change is reflected in lines 615 – 621: “Another important pre-surgical consideration is addressing patient preferences with regards to oophorectomy at the time of hysterectomy as oophorectomy may decrease hormone requirements. Premenopausal oophorectomy at the time of benign hysterectomy in the general population is associated with increased rates of coronary disease, cardiovascular death and dementia. For patients seeking premenopausal oophorectomy and continuing testosterone treatment, the long-term health risks are unclear but should be discussed during the consent process.”

Fertility options for transgender men: No comments

Testosterone and reproduction:
Line 441-442: Consider deleting "or ovarian cysts"

Response: We appreciate the reviewer’s comment. However, we have chosen to keep the report of the result of this study as originally articulated.

Lines 446-452: you make a transition from talking about the effects of testosterone on ovarian function to contraception, but it is not a clear transition. Since there is a segment specifically on contraception, I would remove statements about contraception and stick to stating the unreliable suppression of ovarian function by testosterone and the contraindications to pregnancy with exogenous testosterone.

Response: We agree with the reviewer that moving this statement to the section on contraception is more effective. This change is reflected in the revised manuscript in lines 716 – 720.

Contraceptive Selection:
Lines 462-463: You quote a 32% rate of unintended pregnancies, which is actually better than the overall rate of 47% of pregnancies being unintended. It doesn't clarify the importance of the problem. Maybe compare it to unintended pregnancy rates in other patient populations on medications that are contraindications to pregnancy, such as those on tretinoin etc.

Lines 464-465: Once again, how do these compare to the general population, and if comparable, why is this important (ie why is it more important for this patient population to have more reliable contraception)?
Response: We appreciate the reviewer’s comment. We feel that while 32% is lower than the overall rate of unintended pregnancy, we feel that it still highlights an unmet need for contraception. We specifically discuss the importance of contraception in this patient population given the concern for the teratogenic side effects of testosterone as well as the possibility of worsened gender dysphoria with pregnancy. This is reflected in lines 688 – 690: Selection and appropriate use of effective contraceptive methods is of particular importance for transgender individuals taking gender-affirming hormones and who are concerned pregnancy will worsen feelings of gender dysphoria.

Line 467: replace Efficacy with Effectiveness

Response: We agree with the reviewer’s edit. This is reflected in the manuscript in lines 746 – 748: “In providing contraceptive counseling for this patient population, providers should discuss the effectiveness, ease of use and advantages or disadvantages of contraceptive options for each individual and their gender identity.”

Line 487: replace activing with acting

Response: We agree with the reviewer’s suggested change. This is reflected in lines 761 – 776: “In a survey study of contraceptive preferences among transgender men, 15% of respondents using birth control selected long-acting reversible contraception (LARC) methods with high levels of satisfaction reported among both hormonal and copper IUD users.”

Lines 488-491: Avoid reference to a brand name, given the data supporting comparability of Liletta and Mirena. There are also more recent data for Liletta for menstrual suppression. Provide data supporting use of both and talk more generally about the 52mg Levonorgestrel IUD. Some institutions will only have Liletta available or only Mirena, and it is important that they can be used interchangeably.

Response: We agree with the reviewer. We have therefore placed Mirena with levonorgestrel IUD throughout the manuscript.

Line 494-496: I would reference the ACOG Practice Bulletin on Emergency Contraception

Response: We agree with this suggestion. The practice bulletin was added, reference #78. This change is reflected in lines 782 – 784: “Transgender patients with natal female anatomy should be counseled on and have access to the same options for emergency contraception as cisgender women, including progesterone-only pills, ulipristal acetate and the copper IUD.”

References:

Line 660: is there a follow up publication for this reference? It seems this is a pilot study, and I'm wondering if there is more definitive data published since 2007.

Response: We agree with the reviewer’s suggestion given that the originally cited article was a pilot study from 2007. This citation has been adjusted to reflect the follow-up study with long-term outcomes which was published in 2016. This change is reflected in reference #53.

Lines 729-730: I might also reference the latest edition of the Hatcher text, Contraceptive Technology for this general information and the table on contraceptive options.

Response: We agree with the reviewer that a citation of the Hatcher text, Contraceptive Technology would be a useful addition to the table on contraceptive options. Therefore reference #82 was added.
Lines 731-736: I did not see where these were cited within the text.

Response: We appreciate the reviewer’s comment. These were cited in Table 2.

Table 1: Overall, this is a great inclusion for the manuscript, and very good for practical use.

Progesterone-only contraceptive pills Mechanism: Do you want to list primary and secondary mechanisms and clarify that? I think just listing ovulation suppression is misleading, because this is not a reliable mechanism for these, as it only takes place about 50% of the time. Advantages: with regard to androgenic progestins, this is not very applicable in the US, where POPs only come in one form.

Response: We agree with the reviewer that this discussion of mechanism for progesterone-only contraceptive pills requires clarification. This change is reflected in Table 2 of the revised manuscript.

NuvaRing Disadvantages: You should list thrombotic risk here as well

Response: We agree with the reviewer. We have added thrombotic risk to NuvaRing disadvantages.

You are missing contraceptive patch option

Response: We appreciate the reviewer’s concern. The contraceptive patch was not included given it is an estrogenic form of contraception unlikely to be desired by the transgender or gender non-conforming patient population

Medroxyprogesterone acetate injection Disadvantages: I would not use the word osteoporosis, because that is a specific diagnosis. What is observed is reversible decreased bone mineral density.

Response: We agree with the reviewer that reversible decreased bone mineral density is more accurate than osteoporosis. This change is reflected in the Table 2 of the revised manuscript.

Bilateral tubal ligation: Consider adding to title "permanent contraception." Under disadvantages, I would leave it at impossible to reverse, because reversal is not recommended by most REIs, and very few in the country will perform reversals. This should not be considered in anybody who may want pregnancy in the future.

Response: We appreciate the reviewer’s concern. Given that some practitioners perform tubal reversal, we have made the decision to leave as “difficult if not impossible to reverse.”

Copper IUD: I would separate discussion of Cu IUD for contraception and for emergency contraception. It is confusing that it is only listed under emergency contraception, but then described as both. With regard to emergency contraception mechanism of action, you may want to disclose that this is the only EC option that may prevent implantation of a fertilized egg.

Response: We appreciate the reviewer’s comment. We have clarified use both as planned and as emergency contraception. We prefer to place in the table only once rather than to repeat information. Table 2 is revised to reflect these changes.

Progesterone pill for EC: Clarify that it can be used up to 120 hours post unprotected intercourse, but effectiveness decreases after 72 hours.
Response: We agree with the reviewer's comment. We have clarified this point in Table 2.

Figure 1: No comments.

Reviewer #3: I thank the authors for their paper on an important topic for women's health care providers. While I agree that most primary care providers are not experienced to provide optimal care to the transgender community, this submitted paper is confusing in that it fails to focus on the subject matter communicated by the title of the paper. Accordingly, the authors should consider to pen a systematic review of gynecologic care for transgender individuals or to focus a paper on the title that is found on this submission. The attempt by the authors to provide a comprehensive overview has rendered this paper poorly focused and difficult to follow.

Response: I agree that the title needs to be reframed given the broader coverage in the context of the review. Therefore the review was retitled: Office gynecologic care of transgender and gender non-binary patients: managing vaginal bleeding and contraception

Reviewer #4: Although this is very well-written, I do not think this adds a significant amount to existing literature.

EDITOR COMMENTS:

1. Your paper has terrific content. However, I have to agree with Reviewer 3's comments. Your title suggests that you will be writing about the transman or gender non conforming person with female natal sex who has unexpected vaginal bleeding. While you manuscript includes this information, you also include a great deal of medical, epidemiologic and primary care information such that your paper is unfocused. If you wanted to provide a general guide for the OB GYN (the readers of this journal) for caring for transmen and gender non conforming people with natal female sex anatomy, then you have much more to consider including (mammography? breast binding hows? pregnancy and lactation? violence screening/ PREP?). If you really wanted to focus on vaginal bleeding, you have way too much general information about this population. You really need to decide and then revise your paper--title, abstract, and paper--accordingly.

Response: We agree that the title needs to be reframed given the broader coverage in the context of the review. Therefore the review was retitled: Office gynecologic care of transgender and gender non-binary patients: managing vaginal bleeding and contraception.

2. In addition to the comments from the reviewers above, you are being sent a notated PDF that contains the Editor’s specific comments. Please review and consider the comments in this file prior to submitting your revised manuscript.

***The notated PDF is uploaded to this submission's record in Editorial Manager. If you cannot locate the file, contact Randi Zung and she will send it by email - rzung@greenjournal.org.***

- Although this is not a systematic review and the exact description of the contents of the abstract won't apply, it should still be focused and < = 300 words. As noted by at least one of your reviewers, your article has a lot of general information about transgender health, while your title suggests this paper is about the evaluation of transgender people (it might be useful to say transmen since transwomen don't have uterusus and it
would help the readers get used to what for some is unfamiliar terminology. If you revise your paper to report on the evaluation of transmen with unexpected vaginal bleeding, then your abstract should focus on that.

Response: The pdf uploaded in Editorial Manager was reviewed by the authors. We agree with the concern of the Editor that the title of the original manuscript did not effectively address the content of the manuscript as a whole. We therefore have changed the title in the revised manuscript to Office gynecologic care of transgender and gender non-binary patients: managing vaginal bleeding and contraception. We agree with the editor that the article pertains to transmen and gender non-binary individuals with natal female anatomy, we should clarify this focus in the abstract. This is addressed in lines 35 – 37: Vaginal bleeding in transmen should be evaluated in a similar manner to natal women, and with knowledge of the individual’s present reproductive organs.” Additionally, the following description was added at the end of the first paragraph of the manuscript in lines 122 – 125: “Transgender men and gender non-conforming individuals commonly present to a gynecologist for ambulatory care, while transwomen are much less likely to do so. Therefore, this review will focus on gynecologic care for transgender men and gender non-conforming patients with natal female anatomy.”

- warrants measurement of hormone levels

Response: We agree with the Editor. This change is reflected in lines 37 – 39: “The majority of transmen on gender-affirming hormone therapy will have cessation of menses by six months of continuous use and thus bleeding beyond this interval warrants measurement of hormone levels and further evaluation.”

- can be used

Response: We agree with the Editor’s suggested change. This is reflected in lines 39 – 42: “Progesterone only methods including progesterone only pills, medroxyprogesterone acetate or levonorgesterol IUD can be used in transmen with continued menses despite physiologic testosterone levels or to act as a bridge method for menstrual cessation at the time of testosterone initiation.”

- The Journal style doesn’t not use the virgule (/) except in numeric expressions. Please edit here and in all instances.

- transpeople who have gender affirming surgeries still require hormonal therapy. Shoud this be an "or" or an "And"

Response: We have removed the virgule (/) from the manuscript text. This change is reflected in lines 96 – 97: “Individuals that identify as transgender may seek hormonal, surgical or a combination of gender-affirming modalities.” This changes is reflected in lines 101 – 103: “These efforts range from living with gender incongruence, undergoing a social transition without gender-affirming treatments, pursuing a medical transition with hormones which may include minor surgical procedures or undergoing gender-affirming surgeries.”

- We had a terrific grand rounds at UNC on transmen and pregnancy today and it was the first time I had ever heard of "tucking". It makes sense, I had just never heard the word before. It may be useful to define this a bit more. It was used in the full description of "tucking and taping".
We appreciate the concern by the Editor that readers may not be familiar with the term “tucking”. We have therefore added a description of the process. This change is reflected in lines 171 – 189: “This may include changing hairstyle, adapting clothing style, changing name and pronouns, wearing a binder, use of prosthetics, tucking (a practice of moving natal male anatomy posteriorly to allow for a visibly smooth crotch contour), voice training and beginning the process of resocialization to better match one’s gender identity.”

- appropriate here to ask for what terms transmen use for their anatomy related to the sex? (not gender)

We agree with the Editor that physicians should ask for patient preferences with regards to referring to their anatomy. This change is reflected in lines 279 – 282: “Using the patient’s preferred name and pronouns, discussing the routine nature of screening questions, particularly regarding sexual behavior, asking patients their preferences for referring to their own anatomy, and using gender neutral terminology can help affirm the patient’s gender identity in the clinic setting.”

- while on continuous testosterone therapy

We agree with the Editor that it is important to clarify we are speaking of patients on continuous testosterone therapy in this point. This change in the revised manuscript is reflected in lines 319 – 328: “Patients who have continued vaginal bleeding beyond six months of testosterone therapy or patients on continuous testosterone therapy whose bleeding ceases and then resumes should undergo an examination and further evaluation.”

- work-up is jargon. Consider "evaluation" or "diagnostic evaluation".

We agree with the Editor that “work-up” is jargon. This change has been reflected in lines 319 – 328: “Patients who have continued vaginal bleeding beyond six months of testosterone therapy or patients on continuous testosterone therapy whose bleeding ceases and then resumes should undergo an examination and further evaluation.”

- other than testosterone, are their other gender-affirming hormonal therapies? could you be clear about what hormones you mean rather than using their indication only (gender affirming) please state the types.

We agree with the Editor that it is important to be more specific in regards to the gender-affirming hormones. In the context of transmen and gender non-binary patients discussed in this review article, the masculinizing gender-affirming hormones are testosterone preparations. In the revised manuscript this is further clarified in lines 340 – 341: “Testosterone as masculinizing hormone therapy is available in multiple bioidentical injectable and topical preparations”. We have additionally added Table 1 which includes the types of testosterone preparations as well as dosing information provided by the UCSF Center for Excellence for Transgender Health.

- On the other hand, androgens have been shown....

This contrast was clarified in the revised manuscript in lines 341 – 346: “Historically it was recommended to prescribe testosterone for a limited time prior to gender-affirming surgery due to the theoretical concern that exogenous testosterone can aromatize to estrogen with an increased risk of endometrial hyperplasia and carcinoma. However, more recent data supports the theory that androgens induce a hypoestrogenic state with inhibition of endometrial cell growth and secretor activity and subsequent endometrial atrophy with decreased risk of malignant progression” as well as lines 374 – 376: “These results provide further evidence for an inhibitory rather than stimulatory effect of testosterone on endometrial cell growth.”
- for clarity, would you consider ...have shown upregulation of neither Ki-67...nor ZIC2.

Response: We agree with the Editor that the revised statement is more clear. This change is reflected in lines 372 – 372: "Studies of gene expression in hysterectomy samples of transgender men on testosterone therapy have shown upregulation of neither Ki-67, a marker of mitotic activity, nor ZIC2, a gene associated with endometrial cancer."

- from here to end of paragraph you are not really addressing vaginal bleeding but general health issues.

Response: We appreciate the Editors comment. In this section of the paragraph we aimed to describe other health issues (cervical dysplasia or STIs) which may be a contributory cause to abnormal bleeding in these patients.

- again, if you mean all trans people, fine to use transgender here, but it seems you specifically mean transmen.
If you could be clear about the terminology and use the specific term when you mean it specifically, that would be helpful

Response: We appreciate the Editor’s comment. In this statement we are referring to transgender patients as a whole for whom we would recommend HPV vaccination.

- this patient pop--is that HIV positive or transmen? Please clarify

Response: We agree with the Editor that the described patient population requires further clarity. This change was reflected in the revised manuscript, lines 387 – 389: “Despite this known risk of cervical cancer, transmen are significantly less likely than cisgender women to have pap smears performed and when pap smears are performed results are more likely to be unsatisfactory.”

- if an negative result is obtained on self collected specimen do you recommend a provider obtained specimen?

Response: We feel that in a patient-centered approach to transgender patients it is important that patients are counseled on the specificity and sensitivity of the self-collected HPV swabs and that this is a reasonable alternative to traditional cervical cancer screening. This position is further reflected in the revised manuscript lines 413 – 416: Transgender patients for whom a pap smear or physician-collected HPV swab elicits significant discomfort should be counseled on the sensitivity and specificity of the self-collected HPV swab and offered this method as an alternative screening option”

- Not sure what this means. Other than frank hemorrhage, isn't' most endometrial bleeding breakthroug bleeding from capillaries?

Response: We agree with the Editor that this description for the mechanism of break-through bleeding is not helpful. The revised manuscript reflects this change in lines 502 – 504: “Transgender patients receiving progesterone therapy for menstrual suppression should also be counseled on progestin-only breakthrough bleeding, which often improves with continued use.”

- by my count, this is at least the 3rd time you've mentioned this. Please condense.
Response: We agree with the reviewer that this statement is redundant. It has therefore been removed in the revised manuscript.

- is it not acceptable for transmen testosterone?

Response: We agree with the reviewer that this statement requires further clarity. This change is reflected in the revised manuscript, lines: 553 – 554: “The levonorgesterol IUD is an alternative to systemic hormonal therapy for achieving menstrual cessation.”

3. 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, as well as subsequent author queries. 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:
1. OPT-IN: Yes, please publish my response letter and subsequent email correspondence related to author queries.
2. OPT-OUT: No, please do not publish my response letter and subsequent email correspondence related to author queries.

Response: OPT-IN

4. 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.

Any author agreement forms previously submitted will be superseded by the eCTA. During the resubmission process, you are welcome to remove these PDFs from EM. However, if you prefer, we can remove them for you after submission.

Response: Thank you. The team of authors will plan to complete the eCTA prior to resubmission deadline.

5. Figure 1: Should be a text box instead of a figure. Author also needs to obtain permission to use this source.

Response: This figure was revised to be a text box. Upon receipt of the suggested revisions a request was placed to American Psychiatry Association to obtain permission to use the criteria for gender dysphoria as depicted in Figure 1. A permission grant has been obtained from the American Psychiatry Association.

Tables, figures, and supplemental digital content should be original. The use of borrowed material (eg, lengthy direct quotations, tables, figures, or videos) is discouraged, but should it be considered essential, written permission of the copyright holder must be obtained. Permission is also required for material that has been adapted or modified from another source. Both print and electronic (online) rights must be obtained from the holder of the copyright (often the publisher, not the author), and credit to the original source must be included in your manuscript. Many publishers now have online systems for submitting permissions request; please consult the publisher directly for more information.
6. 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://urldefense.proofpoint.com/v2/url?u=https-3A__www.acog.org_About-2DACOG_ACOG-2DDepartments_Patient-2DSafety-2Dand-2DQuality-reVITALize&d=DwIGaQ&c=imBPVzF25OnBgGmVOlcsieGhHoG1i6YHLR0Sj_gZ4ad&c=r=qgNY7IOAnhehtMe7uOVIYo-ku4X7qS0_f1qYLFYhYhw&m=Kb2q1WQv0AOIYOYgVLsQgI_wvA1FFUg1csRLR2uQc&d=0J-JfYHJJIBBjUKTK304t0FONzODGESaiLmYnDHN2Q&e=. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

Response: the reVITALize definitions were reviewed at the above website. We do not feel that the use of these definitions is problematic.

7. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Review 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.

Response: The word count of our revised manuscript is 6224 words. The review article excluding references is 25 pages.

8. 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).

Response: We have noted the above guidelines.

9. 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.

Response: We have reviewed the abstract and it is consistent with the word count limits of less than 300 words and discusses the context of our review article.

In addition, the abstract length should follow journal guidelines. The word limits for different article types are as follows: Reviews, 300 words. Please provide a word count.
10. Only standard abbreviations and acronyms are allowed. A selected list is available online at https://urldefense.proofpoint.com/v2/url?u=http-3A__edmgr.ovid.com_ong_accounts_abbreviations.pdf&d=DwIGaQ&c=imBPVzF25OnBgGmVOlesiEgHoGl6i6YHLR0Sj_gZ4adc&r=qgNY7IOAnehtMe7uQV1Yo-ku4X7qS0_f1qYL-HyYhfw&m=Kb2q1WQv0A0UY3V4GILsQgI wwA1FFUg1csRLR2uQc&s=Bz66RTVLawCP5IMJPs7RcuOe7HJ3AIWyT9d3Hw-l&c=. 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.

Response: We have reviewed the manuscript and do not use abbreviations or acronyms beyond the selected list.

11. The commercial name (with the generic name in parentheses) may be used once in the body of the manuscript. Use the generic name at each mention thereafter. Commercial names should not be used in the title, précis, or abstract.

Response: We have reviewed the manuscript and do not use commercial names inappropriately.

12. 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.

Response: As noted in the pdf by the Editor, inappropriate use of the virgule symbol (/) has been removed.

13. Please review the journal's Table Checklist to make sure that your tables conform to journal style. The Table Checklist is available online here: https://urldefense.proofpoint.com/v2/url?u=http-3A__edmgr.ovid.com_ong_accounts_table-5Fchecklist.pdf&d=DwIGaQ&c=imBPVzF25OnBgGmVOlesiEgHoGl6i6YHLR0Sj_gZ4adc&r=qgNY7IOAnehtMe7uQV1Yo-ku4X7qS0_f1qYL-HyYhfw&m=Kb2q1WQv0A0UY3V4GILsQgI wwA1FFUg1csRLR2uQc&s=hY7qUjIV3bW6f5bXzQ-kscR5cVFUERdrAP2zLWflXLw&e=.

Response: The Tables in our review article conform to the journal style as described.

14. 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://urldefense.proofpoint.com/v2/url?u=https-3A__www.acog.org_Clinical-2DGuidance-2Dand-2DPublications_Search-2DClinical-
Response: Throughout the article we reference the most updated ACOG documents as pertaining to our topic of discussion.

15. Authors whose manuscripts have been accepted for publication have the option to pay an article processing charge and publish open access. With this choice, articles are made freely available online immediately upon publication. An information sheet is available at https://urldefense.proofpoint.com/v2/url?u=http-3A__links.lww.com_LWW-2DES_A48&d=DwIGaQ&c=imBPVzF25OnBgGmVOLcsiEgHoGli6YHLR0Sj_gZ4adc&r=qqNY7IOAn ehtMe7uOVLYo-ku4X7qS0_f1qYL- HyYhfw&m=Kb2q1WQyo0AUOY3VGILsQglI wwAIFFUg1csRLR2uQc&s=--xQzHzjbhYLSvAoMjF8CiKwznja3tvOTUT1zqvli40s&e=. The cost for publishing an article as open access can be found at https://urldefense.proofpoint.com/v2/url?u=http-3A__edmgr.ovid.com_acd_accounts_ifauth.htm&d=DwIGaQ&c=imBPVzF25OnBgGmVOLcsiEgHoGli6YHLR0Sj_gZ4adc&r=qqNY7IOAn ehtMe7uOVLYo-ku4X7qS0_f1qYL- HyYhfw&m=Kb2q1WQyo0AUOY3VGILsQglI wwAIFFUg1csRLR2uQc&s=--fM1RzVd38UYHYj2Q vSlwjURUbAWdWmfW51cFmS5f2s&e=.

Please note that if your article is accepted, you will receive an email from the editorial office asking you to choose a publication route (traditional or open access). Please keep an eye out for that future email and be sure to respond to it promptly.

16. If you choose to revise your manuscript, please submit your revision via Editorial Manager for Obstetrics & Gynecology at https://urldefense.proofpoint.com/v2/url?u=http-3A__ong.editorialmanager.com&d=DwIGaQ&c=imBPVzF25OnBgGmVOLcsiEgHoGli6YHLR0Sj_gZ4adc&r=qqNY7IOAn ehtMe7uOVLYo-ku4X7qS0_f1qYL- HyYhfw&m=Kb2q1WQyo0AUOY3VGILsQglI wwAIFFUg1csRLR2uQc&s=a5rO80643a6alUo77A1o LWFM2NAzQvNXW-5kSi3IDSk&e=. It is essential that your cover letter list point-by-point the changes made in response to each criticism. Also, please save and submit your manuscript in a word processing format such as Microsoft Word.

Response: We plan to submit a point-by-point document of our changes. We will submit a manuscript revision in Microsoft Word format.

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.

Response: All co-authors have given approval to this revised manuscript.

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 Feb 28, 2019, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,
Nancy C. Chescheir, MD
Editor-in-Chief
Hi Ms. Zung

Given that I have had a difficult time with obtaining a response from the UCSF Center for Transgender Health (original table, Dr. Deutsch) I have reached out again to Dr. Zevin who was the author of the second modified table that I have sent you.

I have heard back from Dr. Zevin with the necessary permission requirements (I am forwarding you that communication) and I would like to proceed with the modified table. I am attaching a word doc of both the modified table and the manuscript with the modified table and appropriate references.

Thank you so much for your time! My apologies on the delay obtaining permission but I am hopeful that the response from Dr. Zevin will satisfy your requirements. Please let me know if there is anything further that I can provide.

All the best,
Amanda
All the best,
Amanda

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From: Randi Zung <RZung@greenjournal.org>
Sent: Wednesday, April 3, 2019 2:52:50 PM
To: Amanda Schwartz
Cc: Denise Shields
Subject: RE: Your Revised Manuscript 19-33R1

Dear Dr. Schwartz:

Apologies for the delay. I have read through all of the messages you’ve sent. Just to confirm, you want to proceed with the original table 1 that is contained in the attached file (vS)?

Regarding the permission letter, is Dr. Deutsch the copyright holder of the source for the table [http://transhealth.ucsf.edu/trans?page=guidelines-masculinizing-therapy](http://transhealth.ucsf.edu/trans?page=guidelines-masculinizing-therapy)? The copyright holder is not necessarily the author of the document. It may actually be her institution. That needs to be clarified.

We need a formal statement from the copyright holder that states you have permission to modify the table, and that you have permission to use this for print publication and electronic publication.

Thanks,
Randi

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From: Amanda Schwartz <Amanda.Schwartz@ucsf.edu>
Sent: Monday, April 1, 2019 2:16 PM
To: Randi Zung <RZung@greenjournal.org>
Subject: Re: Your Revised Manuscript 19-33R1

Hi Ms. Zung,

I wanted to update you that I have finally heard back from the UCSF Center for Transgender Health and Dr. Deutsch who authored the table in our original manuscript on masculinizing hormone therapy. She has granted us permission to use her table in our manuscript. If it is helpful I can resend a copy of the manuscript with this original table. I will additionally forward you our email correspondence. Thank you very much for your time. Please let me know if I can provide anything further.

All the best,
Amanda

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From: Amanda Schwartz
Sent: Thursday, March 28, 2019 4:31:52 PM
To: Randi Zung
Subject: Re: Your Revised Manuscript 19-33R1

Hi Ms. Zung,
I have updated the manuscript draft with the changes to the table. I am attaching the updated manuscript draft here. Please let me know if there is anything further I can send your way!

Thank you,
Amanda

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**From:** Amanda Schwartz  
**Sent:** Thursday, March 28, 2019 4:12:40 PM  
**To:** Randi Zung  
**Subject:** Re: Your Revised Manuscript 19-33R1

Hi Ms. Zung,

Given that we have still not been able to receive permission for Table 1, we have reached out to Dr. Zevin, the medical director for Gender Health for the San Francisco Department of Public Health given that he has a publication with a similar table. I have received permission from him to use the table for the purpose of our article. I have therefore revised the table from the original manuscript to reflect the table from Dr. Zevin. I am attaching the updated table here. I also plan to update the manuscript with this revised table if that would be of use. Additionally I will forward you the correspondence with Dr. Zevin in which he gives permission to reproduce the table.

Thank you,
Amanda

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**From:** Amanda Schwartz  
**Sent:** Wednesday, March 27, 2019 5:57:09 PM  
**To:** Randi Zung  
**Subject:** Re: Your Revised Manuscript 19-33R1

Hi Ms. Zung,

I have not yet heard back but have reached out to additional providers from this publication today. I am hopeful to hear in the coming days.

Thank you,
Amanda

Sent from my iPhone

On Mar 27, 2019, at 11:33 AM, Randi Zung <RZung@greenjournal.org> wrote:

*Dear Dr. Schwartz:*

> Have you received a permission letter for Table 1 yet? The reference is "Center of Excellence for Transgender Health: Guidelines for the Primary and Gender-Affirming Care of Transgender and Gender Nonbinary People."
Hi Ms. Zung,

I have gone through the Editor's comments and I have created an updated manuscript which reflects these recommendations. I am attaching the updated manuscript as well as our line-by-line response to each of the requested changes.

Additionally I have received your email requesting the email correspondence with the representative from the APA and will be forwarding that to you shortly.

Thank you so much for your assistance!

All the best,
Amanda

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Dear Dr. Schwartz:

Dr. Chescheir has reviewed your edited version. She has a few remaining queries for you to address. They are highlighted in blue in the attached file (v4), and listed below:

1. Line 66: Sorry. Could you define what a “gendered person” is? The majority of readers, who you are trying to educate about this issue, will probably be stooped by this. I’ve myself am one of those—as I can’t figure out what a non-gendered person would be. There is a gender spectrum but are there “non gendered” people?

2. Line 140: You do not get to the purported purpose of your paper—a discussion of abnormal bleeding and contraception—until a bit less than ½ way through the document. I don’t think content related to making one’s clinic welcoming particularly relevant to this paper. Nor is the way the diagnosis is made. Please read through the first half and define what of this content is necessary to include to inform the reader about abnormal vaginal bleeding and contraception in transmen and gender non-binary people with a uterus. There will be some content there, such as training sonographers regarding this approach and an emphasis on not inducing gender dysphoria but beyond that this contains way too much general content still. There are other documents that review issues about obstacles to health care, how to set your office to be welcoming, etc. You can reference those, but you don’t need to duplicate the content.
3. Line 200: How do provider assumptions result in safety concerns for these patients?
4. Line 305: Isn’t this cervicitis from the testosterone? Not sure I understand the “therefore” in the next sentence. Seems a non sequitur.
5. Line 343: Do you mean here “less responsive” because they are structural problems or “less responsive” compared to the same findings in a cis-gender person. There are some medications now for fibroids, and UAE; not aware of any non-surgical approach to polyps in any population.
6. Line 421: What about progestin containing IUD?
7. Line 559-560: Please note the Editor’s requested deletion.
8. Line 576: You’ve already listed the prog only contraceptives. It does not need to be repeated here.

Please send your updated file back to me when you are ready. I will be out of the office on March 25, in case you want to use the weekend to work on this.

Thank you,
Randi

From: Amanda Schwartz  
Sent: Wednesday, March 20, 2019 6:45 AM  
To: Randi Zung <RZung@greenjournal.org>  
Subject: Re: Your Revised Manuscript 19-33R1  

Dear Ms. Zung,

Thank you so much for your time and edits. I am sending you our revised manuscript as well as a point-by-point response to each of the recommended changes. Additionally if there is anything further we can supply to assist with the review process please let me know. On that note if you would like a version of the manuscript without tracked changes or if you would prefer to have any of the revisions submitted via the Editorial Manager, I would be happy to do so. We very much appreciate your time and consideration.

With sincere gratitude,
Amanda Schwartz

From: Randi Zung <RZung@greenjournal.org>  
Sent: Thursday, March 14, 2019 11:14:38 AM  
To: [Redacted]; Amanda Schwartz  
Subject: Your Revised Manuscript 19-33R1  

Dear Dr. Schwartz:

Your revised manuscript is being reviewed by the Editors. Before a final decision can be made, we need you to address the following queries. Please make the requested changes to the latest version of your manuscript that is attached to this email. Please track your changes and leave the ones made by the Editorial Office. Please also note your responses to the author queries in your email.
Note: Your manuscript’s article type is going to be changed to Current Commentary. The Review article type is usually reserved for submissions that have followed PRISMA or MOOSE guidelines.

1. General: The Manuscript Editor and Dr. Chescheir have made edits to the manuscript using track changes. Please review them to make sure they are correct.

2. General comment from Dr. Chescheir: Thank you for submitting the revision of your paper. I fear that some of the feedback from reviewers and I may have been misunderstood. We pointed out that your paper was original titled in such a way that the anticipation was that you would be addressing vaginal bleeding and contraception. Instead, the paper originally seemed to be a broad view of the gynecologic care of transgender men and non-binary people with natal female anatomy. You were encouraged to limit your paper to the vaginal bleeding and contraception topics. Your response to these reviews was essentially that you would change the title, which still reflects a focus on the vaginal bleeding and contraceptive needs of this population.

Unfortunately, this did not address the problem of a much broader focus of your paper. If you wish to provide a broad overview of gynecologic health needs of transmen and non-binary people with natal female anatomy, that is a different paper. For this paper, I’ve gone through the current revision and recommended which sections need to be removed. As well, you have several areas where there is significant but unnecessary redundancy and I’ve pointed out where subjects can be condensed.

This is going to require a significant focusing and editing of your paper, some reorganization and strict attention to the references, many of which will not be needed for this paper. I totally get it if this is not of interest to you. I do believe that a well-written, focused review of abnormal vaginal bleeding and contraceptive needs in this population would be a benefit to the practicing doctor.

3. Line 39: Is this statement true just of transgender individuals, or of all individuals?

4. Line 63: The following is the definition from the Sanchez article: “Transgender persons (or transpersons) are individuals who feel an incongruity between their self-identified gender and their birth gender.”

Your version is a bit more confusing to this reader. The idea of a “gendered person” adds a layer to the Sanchez definition that is not clear. Also, what does “or gender identity” go with? What would it be replacing in the first portion of the sentence. In other words, what is it “or” to?

5. Line 66: This sentence seems to be duplicated as far as content is concerned with the information in the next paragraph (highlighted in yellow).

6. Line 70: Please define this term.

7. Line 94: One of the issues with your paper’s organization is that you have similar content spread across this introductory section. I recommend that you outline each paragraph, including having a topic sentence and then have similar content condensed into one place. This paragraph is an example of what I’m talking about. You originally talked about emotional distress, but then you had all the content about the change in DSM V and the issue of distress 2 paragraphs later.
8. Line 96-97: How does this sentence fit into this introductory section about the transgender population?

9. Line 99-102: This sentence (highlighted in yellow) seems pretty similar to content stated earlier in the text.

10. Line 104-105: Can you state the objectives of this review (Primary and any secondary ones) here? We’ve made a suggested edit as an example, but feel free to use something else.

11. Line 148: Not sure what you mean. You don’t say what “inadvertently assumes” something, but it appears to be “a social transition”. A transition cannot assume anything. Who is making these assumptions and how do you know its inadvertent (wrong) about how the person is being perceived and treated.

12. Line 160: I’ve recommended deleting the phrase below as you have not identified “high risk behaviors”. Also, a person is not vulnerable to their own behaviors.

13. Line 168: If you feel that the information from the introduction about insurance is important, you may wish to include it in this section.

14. Line 185: Here is content about provide assumptions again. This section on provider knowledge gaps would be a good place to put all of the information (condensed) about provider assumptions.

15. Line 247-248: This has already been stated earlier in the text. You can delete it from here.

16. Line 273-300: This highlighted section does not pertain to the topic of your paper: managing vaginal bleeding and contraception. It is a general discussion of screening for STIs including HPV related issues. Please limit your review to discussions of vaginal bleeding and contraception. You have not included information about transvaginal ultrasound screening (good idea? Any accommodations? Any concerns?)? What about SIS? Are transmen following testosterone therapy at higher risk than cis-women for cervical stenosis that might make this hard? What does a gender-affirming hormonal milieu do to some of the evaluation for hormonal causes of abnormal vaginal bleeding (prolactin? Etc) My suggestion at this point is that to be helpful to the doc in practice, go through the typical algorithms for work up of abnormal vaginal bleeding in an adult cis-woman. Then, go through each step and tell us which steps might need to be interpreted or performed differently, such as my questions above.

17. Line 303: I’ve moved this here as it is about managing vaginal bleeding so should go in this section, not in the section on menstrual suppression.

18. Line 334: This section, pubertal suppression, is not related to the topic of your paper. Please delete.

19. Line 366-371: This information can be moved to the menstrual suppression section.

20. Line 391: Please note this edit.
21. Line 445: Fertility options are part of vaginal bleeding or contraception. Please delete.

22. Line 474: Testosterone and reproduction are not part of vaginal bleeding and contraception. Except as it relates to the importance of contraception while on testosterone and the fact that testosterone is not a contraceptive. Please delete.

23. Line 502: You have mentioned this earlier in the text. Please condense this information.


25. Page 33: (Table 1 Reference 17): Please provide a permission from the publisher of this document (for print and online use) to include this information in your article.

26. Page 36 (Box 1): Please provide copies of the pages you used to create this box. We will let you know if you need to seek permission to reprint this information.

To facilitate the review process, we would appreciate receiving a response by March 20.

Best,
Randi Zung

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Randi Zung (Ms.)
Editorial Administrator  |  Obstetrics & Gynecology
American College of Obstetricians and Gynecologists
409 12th Street, SW
Washington, DC 20024-2188
http://www.greenjournal.org
1. General: The Manuscript Editor and Dr. Chescheir have made edits to the manuscript using track changes. Please review them to make sure they are correct.

2. General comment from Dr. Chescheir: Thank you for submitting the revision of your paper. I fear that some of the feedback from reviewers and I may have been misunderstood. We pointed out that your paper was original titled in such a way that the anticipation was that you would be addressing vaginal bleeding and contraception. Instead, the paper originally seemed to be a broad view of the gynecologic care of transgender men and non-binary people with natal female anatomy. You were encouraged to limit your paper to the vaginal bleeding and contraceptive needs of this population.

Unfortunately, this did not address the problem of a much broader focus of your paper. If you wish to provide a broad overview of gynecologic health needs of transmen and non-binary people with natal female anatomy, that is a different paper. For this paper, I've gone through the current revision and recommended which sections need to be removed. As well, you have several areas where there is significant but unnecessary redundancy and I've pointed out where subjects can be condensed.

This is going to require a significant focusing and editing of your paper, some reorganization and strict attention to the references, many of which will not be needed for this paper. I totally get it if this is not of interest to you. I do believe that a well-written, focused review of abnormal vaginal bleeding and contraceptive needs in this population would be a benefit to the practicing doctor.

Response: Thank you for further clarifying your request. We agree with the Editor that a more focused review of bleeding and contraceptive care for transgender individuals would be useful to the readers and have edits this version of the manuscript to further reflect that focus. Additionally, we have changed the title to reflect this refined focus. In an effort to focus on vaginal bleeding and contraceptive care, we have limited our background section on transgender patients with removal of the section on prevalence and refining the section on health care barriers.

We also agree with the Editor that there were areas of the paper, particularly in the introduction section, which were redundant and have revised that to provide further clarity. The sections of the paper which do not reflect this focus were removed in this revised version and the references edited as such.

3. Line 39: Is this statement true just of transgender individuals, or of all individuals?

Response: We agree with the Editor that we would recommend this approach to caring for all patients. The revised manuscript reflects this change in lines 44 – 46: “As with all patients, a thorough patient history with avoidance of assumptions of sexual orientation based on gender identity is integral to providing competent care for transgender individuals”.

4. Line 63: The following is the definition from the Sanchez article: “Transgender persons (or transpersons) are individuals who feel an incongruity between their sex and gender they were assigned at birth and their internal sense of themselves as a gendered person.”

Your version is a bit more confusing to this reader. The idea of a “gendered person” adds a layer to the Sanchez definition that is not clear. Also, what does “or gender identity” go with? What would it be replacing in the first portion of the sentence. In other words, what is it “or” to?

Response: We agree with the Editor that this definition may be confusion to readers. This has been edited in the revised manuscript which is reflected in lines 76 – 77: “Transgender individuals feel an incongruity between the sex and gender they were assigned at birth and their internal sense of themselves as a gendered person”.

5. Line 66: This sentence seems to be duplicated as far as content is concerned with the information in the next paragraph (highlighted in yellow).

Response: We agree with the Editor that this statement is redundant. We have therefore removed this sentence from line 80 as it is stated in the following paragraph.
6. Line 70: Please define this term.

Response: We agree with the Editor that a definition of gender fluid would be useful. This is reflected in the revised manuscript in lines 83 – 87: “It is important as clinicians to recognize not only the wide spectrum of gender identities along the gender continuum including gender fluid (which describes an individual whose gender identity is not fixed) and non-binary identities, but the varying and very personal steps transgender people may pursue in their effort to align their outward appearance with their sense of self”. This definition was obtained from the National LGBT Health Education Center, cited in reference #2.

7. Line 94: One of the issues with your paper’s organization is that you have similar content spread across this introductory section. I recommend that you outline each paragraph, including having a topic sentence and then have similar content condensed into one place. This paragraph is an example of what I’m talking about. You originally talked about emotional distress, but then you had all the content about the change in DSM V and the issue of distress 2 paragraphs later.

Response: We agree with the Editor that this introductory section needs structural improvement. We have therefore revised the second and third paragraphs of the section to have a clearer focus which is reflected in the topic sentences of the paragraph.

8. Line 96-97: How does this sentence fit into this introductory section about the transgender population?

Response: We agree with the Editor that this statement is an outlier in this section and it was therefore removed.

9. Line 99-102: This sentence (highlighted in yellow) seems pretty similar to content stated earlier in the text.

Response: We agree with the Editor that this statement is redundant and it has therefore been removed.

10. Line 104-105: Can you state the objectives of this review (Primary and any secondary ones) here? We’ve made a suggested edit as an example, but feel free to use something else.

Response: We agree with the Editor that a clearer statement of our paper’s objectives would be helpful to the reader. This is reflected in lines 132 – 136: “The primary objective of this review is to focus on gynecologic care for transgender men and gender non-conforming patients with natal female anatomy. In this review we discuss a patient-centered approach to the management of vaginal bleeding and contraceptive care for transgender and gender non-binary individuals in a manner which affirms their gender identity”.

11. Line 148: Not sure what you mean. You don’t say what “inadvertently assumes” something, but it appears to be “a social transition”. A transition cannot assume anything. Who is making these assumptions and how do you know its inadvertent (wrong) about how the person is being perceived and treated.

Response: We agree with the Editor that the wording of this sentence is confusing. It has been revised in the updated manuscript as seen in lines 213- 217 “A social transition aims to elucidate the severity of the gender dysphoria and potential benefit from gender-affirming treatments. A goal of this social transition period is for the individual to be perceived and treated by others as the gender with which they identify, though the way in which society interacts with the individual can be variable”.

12. Line 160: I’ve recommended deleting the phrase below as you have not identified “high risk behaviors”. Also, a person is not vulnerable to their own behaviors.

Response: We agree with this recommendation. In refining our focus of this review to vaginal bleeding and contraception we have removed this from the background section.

13. Line 168: If you feel that the information from the introduction about insurance is important, you may wish to include it in this section.

Response: We do not feel that the insurance information is critical to the focus of this review.
14. Line 185: Here is content about provide assumptions again. This section on provider knowledge gaps would be a good place to put all of the information (condensed) about provider assumptions.

Response: We agree that the discussion of provider assumptions two paragraphs below is redundant and we have therefore deleted the repetitive statement. The discussion of provider understanding of the gender continuum we feel should remain in the introduction section where the gender continuum is discussed and terminology defined.

15. Line 247-248: This has already been stated earlier in the text. You can delete it from here.

Response: We agree with the Editor that the statement of evaluation similar to cisgender women is redundant, therefore this was removed from the topic sentence of this paragraph.

16. Line 273-300: This highlighted section does not pertain to the topic of your paper: managing vaginal bleeding and contraception. It is a general discussion of screening for STI’s including HPV related issues. Please limit your review to discussions of vaginal bleeding and contraception.

Response: We agree with the Editor that this section pertains more towards generalized gynecologic care for transgender individuals and was therefore removed. We do feel that transgender individuals with vaginal bleeding should be evaluated for STIs in their workup and an examination performed with visualization of the cervix given the rare but documented risk of cervical cancer.

You have not included information about transvaginal ultrasound screening (good idea? Any accommodations? Any concerns?)? What about SIS? Are transmen following testosterone therapy at higher risk than cis-women for cervical stenosis that might make this hard? What does a gender-affirming hormonal milieu do to some of the evaluation for hormonal causes of abnormal vaginal bleeding (prolactin? Etc) My suggestion at this point is that to be helpful to the doc in practice, go through the typical algorithms for work up of abnormal vaginal bleeding in an adult cis-woman. Then, go through each step and tell us which steps might need to be interpreted or performed differently, such as my questions above.

Response: We agree with the Editor that more information regarding the approach to applying vaginal bleeding algorithms for this patient population. We have read through the suggested areas of inquiry by the Editor and have included our recommendations in lines 336 – 350: “In evaluation of structural causes of abnormal uterine bleeding, a special consideration for this patient population includes an understanding that undergoing a transvaginal ultrasound can promote gender dysphoria. While transvaginal ultrasound imaging is part of the algorithm for management of abnormal bleeding, based on our experience transabdominal imaging may be considered in transgender or gender non-binary patients if the uterus is able to be adequately visualized. For patients in whom a transvaginal ultrasound is necessary, counseling should be provided for the patient and imaging should be performed by gynecologists or ultrasonographers trained in providing competent gender-affirming care. Providers may also consider a low-dose benzodiazepine, such as 0.5 mg lorazepam, given orally 30 minutes prior to the procedure in coordination with administration of 2-5% lidocaine ointment applied to the vulva and vagina as well as offering patients the option of placing the probe intra-vaginally themselves. In addition to use of transabdominal ultrasound, other non-invasive diagnostic options such as expectant management for induction of amenorrhea 6 months after testosterone initiation or observation for a withdrawal bleed after a progestin challenge may be considered in this patient population”.

With regards to a saline-infused sonohysterogram, that would likewise require transvaginal imaging and would have similar concerns as discussed above. In our practice experience as well as through a literature review we have not found significant concerns with regards to cervical stenosis and any limitation that this may have in the evaluation of abnormal uterine bleeding. In our practice, cervical stenosis has not been a limiting factor in the performance of endometrial biopsies or IUD placement for our transgender and non-binary patients. Other than contributing to unsatisfactory pap smear results as a result of atrophic changes, we have also not found gender-affirming hormones to negatively impact diagnostic testing in this patient population.
17. Line 303: I’ve moved this here as it is about managing vaginal bleeding so should go in this section, not in the section on menstrual suppression.

Response: We agree with this recommendation.

18. Line 334: This section, pubertal suppression, is not related to the topic of your paper. Please delete.

Response: We agree with this recommendation and have removed this section.

19. Line 366-371: This information can be moved to the menstrual suppression section.

Response: We agree with this recommendation. We elected to move discussion of progesterone only methods in transgender adolescents desiring menstrual suppression to the beginning of the menstrual suppression section.

20. Line 391: Please note this edit.

Response: We agree with this change.

21. Line 445: Fertility options are part of vaginal bleeding or contraception. Please delete.

Response: We agree with the reviewer that this section does not fit in the refined focus of the review and it was therefore removed.

22. Line 474: Testosterone and reproduction are not part of vaginal bleeding and contraception. Except as it relates to the importance of contraception while on testosterone and the fact that testosterone is not a contraceptive. Please delete.

Response: We agree with the reviewer. We have therefore removed the majority of this section. The discussion of contraception on testosterone and that testosterone is not a contraceptive remain in the below section on contraception.

23. Line 502: You have mentioned this earlier in the text. Please condense this information.

Response: We agree with the Editor. With the removal of the section on testosterone and reproduction this no longer feels redundant.


Response: We agree with this replacement and it supports our statement.

25. Page 33: (Table 1 Reference 17): Please provide a permission from the publisher of this document (for print and online use) to include this information in your article.

Response: I have requested permission from the publisher of this document. We are currently awaiting a response.

26. Page 36 (Box 1): Please provide copies of the pages you used to create this box. We will let you know if you need to seek permission to reprint this information.

Response: In the previous revisions, permission was requested for use of this information. I have obtained permission to reprint this information from the American Psychiatric Association. The page numbers for the criteria for gender dysphoria are 451 – 460. If copies of the pages are still requested, please let me know and I would be happy to supply them.

To facilitate the review process, we would appreciate receiving a response by March 20.
Response: We will send our response by 3/20
1. Line 66: Sorry. Could you define what a “gendered person” is? The majority of readers, who you are trying to educate about this issue, will probably be stooped by this. I’ve myself am one of those—as I can’t figure out what a non-gendered person would be. There is a gender spectrum but are there “non gendered” people?

Response: We agree with the Editor that this term may be confusing to readers. We have therefore removed the term gendered person. This change is reflected in the revised manuscript in lines 98 – 99: “Transgender individuals feel an incongruity between the sex and gender they were assigned at birth and their internal sense of gender identity”.

2. Line 140: You do not get to the purported purpose of your paper—a discussion of abnormal bleeding and contraception—until a bit less than ½ way through the document. I don’t think content related to making one’s clinic welcoming particularly relevant to this paper. Nor is the way the diagnosis is made. Please read through the first half and define what of this content is necessary to include to inform the reader about abnormal vaginal bleeding and contraception in transmen and gender non-binary people with a uterus. There will be some content there, such as training sonographers regarding this approach and an emphasis on not inducing gender dysphoria but beyond that this contains way too much general content still. There are other documents that review issues about obstacles to health care, how to set your office to be welcoming, etc. You can reference those, but you don’t need to duplicate the content.

Response: We agree with the Editor that there was too much introductory material prior to discussion of abnormal bleeding and contraception. As requested the section pertaining to clinic-level adjustments to create a safe environment for transgender and gender non-binary patients was removed. Additionally, discussion of healthcare barriers for transgender individuals was significantly reduced. The discussion on the Endocrine Society and WPATH recommendations for diagnosis was also decreased. The content of the introduction was decreased from about 5.5 pages in the prior version to approximately 3.75 pages in the updated manuscript.

3. Line 200: How do provider assumptions result in safety concerns for these patients?

Response: We agree with the Editor that this statement was not clear. In an effort to provide a more concise introductory section prior to discussion of bleeding / contraceptive care, this statement was removed.

4. Line 305: Isn’t this cervicitis from the testosterone? Not sure I understand the “therefore” in the next sentence. Seems a non sequitur.

We agree with the Editor that the way in which this was worded initially is inappropriate. This statement was revised in the updated manuscript as reflected in lines 437 – 439: “Testosterone has a hypoestrogenic effect on vaginal tissue which promotes vaginal atrophy with an increased risk of vaginitis and cervicitis. Given these risks for infection, STI testing and an evaluation for cervicitis should be performed in transgender men with vaginal bleeding”.

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5. Line 343: Do you mean here “less responsive” because they are structural problems or “less responsive” compared to the same findings in a cis-gender person. There are some medications now for fibroids, and UAE; not aware of any non-surgical approach to polyps in any population.

Response: We agree with the Editor that this statement is unclear. The goal here was to communicate that structural causes of abnormal uterine bleeding, may not respond to medical therapy and as in cis-gender women may require surgical management. We agree that polyps causing bleeding should be managed surgically. In the updated manuscript this clarification is reflected in lines 446 - 513: “If the patient presents with a bleeding pattern that is abnormal or changed, providers should consider structural causes such as fibroids which, as in cisgender women, may be less responsive to medical therapy”.

6. Lines 415 – 419: This isn’t clear to me. You’ve set this paragraph up as saying if you have bleeding after amenorrhea 6 months after initiating testosterone. Here you seem to be suggesting that one approach is to wait to see if after 6 months of testosterone does he become amenorrheic. Also this approach is not the standard approach you’ve recommended for natal women. You say earlier you recommend using the same approach, please clarify.

Response: We agree with the Editor that the recommendation to pursue further evaluation if testosterone was not achieved after 6 months was already presented. Here using that to describe a non-invasive diagnostic approach is confusing. This statement was therefore revised in the updated manuscript which is reflected in lines 400 - 403: “In addition to use of transabdominal ultrasound, observation for a withdraw bleed after a progestin challenge may be considered as a non-invasive diagnostic option in this patient population”. Our goal with this recommendation is not to stray from recommendations for natal women but to recognize an alternative consideration for patients that experience significant gender dysphoria with more invasive testing.

7. Line 421: What about progestin containing IUD?

Response: We agree with the Editor that the progestin containing IUD is a valuable option in these patients with menorrhagia requiring a higher dose local progesterone. This is more clearly written in the revised manuscript in lines 551 – 553: “Obtaining a menstrual history in transgender adolescent’s assigned female at birth is imperative, as patients with menorrhagia are more likely to require a higher dose local progesterone, such as the levonorgestrol IUD, to achieve amenorrhea”.

8. Line 559-560: Please note the Editor’s requested deletion.

Response: It appears that the phrase “status post” was removed. We accept this deletion. In the revised manuscript this change is reflected in lines 517 – 519: “According to a national transgender discrimination survey, 21% of transgender men had had a hysterectomy with another 58% desiring a hysterectomy in the future”.

Response: We agree with the Editor’s deletion which is reflected in lines 847 – 849: “Providers must dispel the myth that testosterone can be used for contraception and discuss the importance of reliable contraception for patients receiving gender-affirming hormone therapy”.

9. Line 576: You’ve already listed the prog only contraceptives. It does not need to be repeated here.

Response: We agree with the Editor that listing the progesterone-only contraceptive methods here is redundant. This has been removed and the change reflected in the revised manuscript in lines 857 – 858: “Progesterone contraceptive options have been well tolerated among transgender men”.