OBSTETRICS & GYNECOLOGY

NOTICE: This document contains correspondence generated during peer review and subsequent revisions but before transmittal to production for composition and copyediting:

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

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

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

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

Date: May 24, 2019
To: "Aaron Lazorwitz" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-19-754

RE: Manuscript Number ONG-19-754

Relationship Between Etonogestrel Concentrations and Bleeding Patterns in Contraceptive Implant Users

Dear Dr. Lazorwitz:

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

REVIEWER COMMENTS:

Reviewer #1: In this manuscript, the authors present a cross-sectional study among women with an etonogestrel implant comparing their bleeding patterns with circulating progestin concentrations. Given irregular bleeding is an important complaint among users of this contraceptive approach (leading to 11% quitting the method due to this problem), sorting out potential causes for the irregularity is important. The study found increased concentrations of etonogestrel were linked to abnormal bleeding. Overall the question is reasonable and the approach is overall sound IF self-reported menstrual symptoms are reliable. I have the following specific questions/comments:

1) Line 46 - Abstract - …reported experiencing… Syntax problem.

2) Line 48 - Abstract - What % of subjects had available medical records? The sentence is a bit confusing insofar as you're not saying 20% had available medical records but that's what initially is conveyed.

3) Introduction - 3 paragraphs, nice!

4) Line 101 - Methods - How relatively steady is the steady state achieved at 2 years of etonorgestrel use? Can you be more specific?

5) Line 106 - Methods - Reported medical conditions? Is this reported in the medical record or per the patient or both?

6) Line 108-109 - Methods - Thus this paper is an LPU (least publishable unit)? It least it would be nice to give the name of this larger pharmacogenomic study. Is this study funded by industry?

7) Much of the outcomes measured are from patient self-report. This can be reliable and it can also not be reliable. Are there any data to inform the general reliability of patient recall for the measured bleeding characteristics? I'm reminded of a study that looked at mood and the timing of menses. When the subjects keep a mood diary they found NO association between mood and onset of menses but when the same subjects were given a calendar to recall their mood they consistently recalled being unhappier around the time of their menses. This kind of result makes me nervous about the general reliability of recalled menstrual symptoms.

8) Line 146 - "Sample size was determined by the primary pharmacogenomic outcome." What? Does this mean the size of this sample was fixed by the other study this was part of OR that the pharmacology features determined the sample size OR something else?

9) Line 168 - "Prodrug" Remember the readership…define.

10) Lines 210 - 217 - I'm thinking you're trying to point out the irony that if AA women are 2x more likely to have monthly periods, then why are they 4x more likely to get an Rx for OCPs? If that's correct, then make this point a bit more strongly. A control group of non-etonorgetrel users would be nice to see if this sort of race-based menstrual symptoms extends across a different contraceptive context.

Overall, pretty simple study that appears to offer new insights into a clinically relevant problem.

Reviewer #2: Relationship Between Etonogestrel Concentrations and Bleeding Patterns in Contraceptive implant users

This is a cross-sectional sub-study examining women 18-45 years old who have had a contraceptive implant for at least 12 to 36 months. Participants completed a questionnaire regarding bleeding patterns and had a single blood sample drawn for etonogestrel level. The authors hypothesized that increased serum etonogestrel concentrations would increase abnormal or bothersome bleeding with the contraceptive implant.

Materials and Methods

1. Line 112: Were participants compensated for participation?

2. Line 116: It would be helpful to include the questionnaire that patients completed as a supplement.

3. Line 118: "Abnormal bleeding" is a subjective description. Was a definition provided for participants within the body of the questionnaire?

4. Line 120-121: How did the authors define monthly period and days of bleeding or spotting over 90-day period? There could be significant overlap with days of bleeding vs. monthly period. Or, were days of bleeding included in the definition with bleeding from menstruation?

5. Line 121: Why did the authors choose 90 days? Was this derived from the Belsey criteria?

6. Lines 145-146: In their related paper Smith et al (2019), the authors conduct a careful power analysis to ensure that their statistical analysis possesses sufficient statistical power. Did the authors conduct a similar analysis for the hypotheses tested in this paper? Is this study adequately powered to detect the outcome of interest? A discussion of this issue would be helpful for readers.

Results:

7. Line 155: The authors report the median serum etonogestrel concentration. It would be helpful to place this in a table for the reader.

Discussion:

8. Line 197: Would add a woman is more likely to receive a prescription for management of bothersome bleeding at the Anschutz clinic. This management may not be generalizable to other clinics as other first-line methods include NSAIDs or other hormonal methods.

9. Lines 225-227: The authors conclude the prevalence of bothersome bleeding and overall bleeding patterns are more likely to be representative of the general population of implant users is inaccurate as first-year users are excluded. This should be rephrased.

10. Line 232-235: The authors obtained confirmatory chart information for only 25% of participants (53 out of 208), which should be specifically clarified in their limitations section.

Additional Comments:

11. Readers do not have access to the questionnaire and therefore do not know exactly what "abnormal bleeding" means. Please comment on the decision to ask patients if they had this type of bleeding versus asking participants about the number of days of bleeding.

12. As the authors mention in the Introduction, per Grunloh et. al, the majority of women who discontinued the implant did so in the first 6 months of use. These data would be valuable for patients and practitioners. Why did the authors choose to not evaluate users in the first year of use?

Reviewer #3: In this cross-sectional study of women using the etonogestrel contraceptive implant presenting for routine contraceptive care or recruited through advertising, those with higher serum etonogestrel levels were found to have higher

odds of abnormal bleeding as well as higher odds of treatment for abnormal bleeding.

Introduction

1) line 92-94: is there any basis for the hypothesis that higher etonogestrel concentrations may be associated with abnormal bleeding?

Methods

2) Line 121: the patient survey asked the number of bleeding/spotting days over a 3-month period. Please specify if this meant the last 90 days prior to study enrollment, or some other 90-day period.

3) Line 127: note that the CDC Selected Practice Recommendations also suggests a trial of NSAIDs for treatment of bothersome bleeding, not just a standard treatment with COCs or estrogen

Results

4) Line 151/Table 1: confirm that months of implant use is 25.7 months (per text line 151) vs. 26.0 months (per Table 1)

5) Table 1: confirm that median BMI is 25.7 kg/m2, as the 25.7 number is described within the manuscript as the duration of implant use

6) Table 2: clarify within table caption where there is overlap inn patient self-report of bleeding patterns. For example, are there patients included in the "abnormal bleeding" group who also have a "current monthly period"? The survey questions reflect different timelines, but the data presentation in Table 2 implies mutually exclusive categories.

7) Table 3: consider presenting regression coefficients for all characteristics and demographic variables of interest that were used in the MLR (age, months of implant use, BMI, race, ethnicity, serum ENG concentration).

Discussion

8) Line 194-195: while OR is 1.6 for abnormal bleeding for every 100 pg/mL increase in serum ENG concentration, is this ENG concentration variability likely to be seen in a population? In this study, the IQR of serum ENG concentration is only 63 pg/L, while the majority (59%) experienced abnormal bleeding at some point during their implant use.

9) Add comments on how this paper relates to your similar paper on patient characteristics & serum ENG concentration that published in the April Contraception journal.

STATISTICAL EDITOR'S COMMENTS:

1. lines 53-55: See later comments re: use of the aORs, but for this sentence, the model actually predicts increase in odds, not 1.6 times more likely, but 1.6x the odds.

2. lines 155-156: The distribution of serum etonogestrel appears skewed. Did the Authors attempt to normalize the distribution by transforming the data, eg, log or other methods? The relationship with the outcomes may not depend on the serum concentration linearly.

3. lines 169-187: Need to show more analysis of the relationship between level of circulating progestin and (1) BMI, (2) time since implant and (3) race/ethnicity. Did the racial groups have statistically equivalent time since implant and BMIs? Or, did the level of progestin decrease as the time since implant increased? Similarly, did the progestin level vary inversely with the woman's BMI? Were the follow-up times equivalent for strata based on race? The occurrence of abnormal bleeding or of amenorrhea might be time-dependent, that is, if the follow-up were longer for a particular group, then there would be more time for that side effect/bleeding pattern to manifest. If in fact there were differences in timing, then hazard rate ratios would be the appropriate stats test.

4. Table 3: Should include crude ORs to contrast with the aORs. Need to include more of crude ORs/aoRs in terms of serum etonogestrel concentration vs BMI, time since implant, race etc (which could be a separate Table, if desired.) The aORs need further explanation of their referents. For example, the aOR for abn bleeding was 1.005, but that is per 1 pg/mL. That is a perfectly valid metric for the model, but not very useful clinically, since the logistic model increase would be multiplicative per each 1 pg/mL. Instead, the reference in the Abstract seems more clinically useful. That is, for each 100pg/mL increase in serum estonogestrel concentration, the adjusted
odds of abnormal bleeding increased 1.6 x (then insert CIs), which I believe from the Table would be [1.1,2.2]. Similarly for likelihood of a Rx the aOR per 100 pg/mL would be 2.2 [1.3,3.6]. Also, need to show the referent for the duration, which I believe was per month beyond 12 months (the lower range of the distribution).

5. Since there were 350 women altogether and of those 40 were Black of African American and among the 350, only about

20% receive oral contraception, the number of Black women receiving OC is likely ~ 10. That is too few to allow for multivariable adjustment, due to potential over fitting of the model. Likewise for the entire cohort of 350, only 19 women were Asian or Pacific Islander. That is too few to allow for multivariable adjustment, also. Also, what were the counts for amenorrhea for the Asian and Pacific Islander and for the other racial groups? Since overall there were 52 instances of amenorrhea (15%), I suspect the counts were low for that racial group and again, the model is over fitted.

EDITORIAL OFFICE COMMENTS:

1. The Editors of Obstetrics & Gynecology are seeking to increase transparency around its peer-review process, in line with efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online. Additionally, unless you choose to opt out, we will also be including your point-by-point response to the revision letter, 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:
A. OPT-IN: Yes, please publish my response letter and subsequent email correspondence related to author queries.
B. OPT-OUT: No, please do not publish my response letter and subsequent email correspondence related to author queries.

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

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.

3. Clinical trials submitted to the journal as of July 1, 2018, must include a data sharing statement. The statement should indicate 1) whether individual deidentified participant data (including data dictionaries) will be shared; 2) what data in particular will be shared; 3) whether additional, related documents will be available (eg, study protocol, statistical analysis plan, etc.); 4) when the data will become available and for how long; and 5) by what access criteria data will be shared (including with whom, for what types of analyses, and by what mechanism). Responses to the five bullet points should be provided in a box at the end of the Methods section.

4. All submissions that are considered for potential publication are run through CrossCheck for originality. The following lines of text match too closely to previously published works. Variance is needed in the following sections:
a. Lines 90-2 (“The etonogestrel contraceptive…of protocol adherence.”)
b. Lines 97-98 (“In this cross-sectional…with abnormal metabolism.” Please also note that these methods have been described before- https://www.sciencedirect.com/science/article/pii/S0010782419301234?via%3Dihub
c. Lines 129-137 (“We also collected a single….250, and 350 participants”).

5. 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.

6. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Original Research reports should not exceed 22 typed, double-spaced pages (5,500 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, tables, boxes, figure legends, and print appendixes) but exclude references.

7. 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).

8. 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: Original Research articles, 300 words. Please provide a word count.

9. Abstracts for all randomized, controlled trials should be structured according to the journal's standard format. The Methods section should include the primary outcome and sample size justification. The Results section should begin with the dates of enrollment to the study, a description of demographics, and the primary outcome analysis. Please review the sample abstract that is located online here: http://edmgr.ovid.com/ong/accounts/sampleabstract_RCT.pdf. Please edit your abstract as needed.

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 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.

12. 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.

13. 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.

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

Sincerely,

The Editors of Obstetrics & Gynecology

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

_____

University of Colorado
Anschutz Medical Campus

[redacted]

June 12th, 2019

Dear Editors and reviewers,

Thank you for your review and consideration of our original research article "Relationship Between Etonogestrel Concentrations and Bleeding Patterns in Contraceptive Implant Users." We are excited to resubmit the edited manuscript for publication in *Obstetrics & Gynecology*.

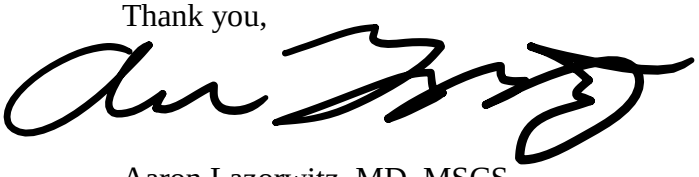
We greatly appreciate the Editor's and reviewers' time and the valuable feedback provided. We have edited the manuscript based on these comments and have included our responses to these comments in this cover letter. Our responses are bolded below.

This manuscript is not under consideration elsewhere and will not be submitted elsewhere until a final decision is made by the editors of *Obstetrics & Gynecology*. **The lead author [Dr. Aaron Lazorwitz] affirms that this manuscript is an honest, accurate, and transparent account of the 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.** This study was approved by the Colorado Multiple Institutional Review Board and all participants gave written informed consent at enrollment. This study is registered on clinicaltrials.gov (ID: NCT03092037).

Dr. Teal has served on scientific advisory boards of Allergan and Bayer Healthcare, and serves on a Data Monitoring Board for a study funded by Merck and Co. Dr. Teal and Dr. Lazorwitz receive research funding from Merck and Co. for an Investigator Initiated Study on drug-drug interactions with the etonogestrel contraceptive implant. The University of Colorado Department of Obstetrics and Gynecology has received research funding from Bayer, Agile Therapeutics, Merck and Co, and Medicines360. The authors have no other conflicts of interest to disclose.

I appreciate the time and considerations invested into this review and look forward to your response. All authors have fulfilled the requirements for authorship and confirmed submission.

Thank you,



Aaron Lazorwitz, MD, MSCS
Principal Investigator

REVIEWER COMMENTS and **Author responses**:

Reviewer #1:

In this manuscript, the authors present a cross-sectional study among women with an etonogestrel implant comparing their bleeding patterns with circulating progestin concentrations. Given irregular bleeding is an important complaint among users of this contraceptive approach (leading to 11% quitting the method due to this problem), sorting out potential causes for the irregularity is important. The study found increased concentrations of etonogestrel were linked to abnormal bleeding. Overall the question is reasonable and the approach is overall sound IF self-reported menstrual symptoms are reliable. I have the following specific questions/comments:

Thank you for your questions and comments.

1) Line 46 - Abstract - …reported experiencing… Syntax problem.

We have corrected this syntax to now read "reported having experienced…" (Line 46)

2) Line 48 - Abstract - What % of subjects had available medical records? The sentence is a bit confusing insofar as you're not saying 20% had available medical records but that's what initially is conveyed.

253 out of 350 participants had available medical records (72.3%). We apologize for the confusion and have changed this sentence to now read: "Among participants with reviewable medical records (n=253), roughly 20% had received a prescription for oral contraceptive pills during implant use." (Lines 48-49)

3) Introduction - 3 paragraphs, nice!

Thank you for your comment!

4) Line 101 - Methods - How relatively steady is the steady state achieved at 2 years of etonorgestrel use? Can you be more specific?

Based on available pharmacokinetic data, we know that the amount of etonogestrel released from the implant is roughly 40ug/day at 1 year of use, 34ug/day at 2 years of use, and 25-30ug/day at 3 years of use. Thus, there is only a 15% total drop in the etonogestrel release rate over the course of 12 months (between years 1 and 2). As comparison, the release rate after four weeks is 60-70ug/day, thus there is up to a 33% drop in release rate over the first year of use. We have added a line to the manuscript to provide this specific information: "From the available pharmacokinetic data, the amount of etonogestrel released from the implant decreases by only 15% on average between 1 and 2 years of use (40ug per day versus 34ug per day), as compared to a decrease of up to 33% between 4 weeks (60-70ug per day) and 1 year of use (14)." (Lines 102-105)

5) Line 106 - Methods - Reported medical conditions? Is this reported in the medical record or per the patient or both?

This was based on patient report. We have revised this line to better reflect this. "We also excluded women who reported any medical conditions …" (Line 108-109)

6) Line 108-109 - Methods - Thus this paper is an LPU (least publishable unit)? It least it would be nice to give the name of this larger pharmacogenomic study. Is this study funded by industry?

We humbly disagree that this manuscript is an LPU. This was a pre-specified secondary outcome of our study, whose primary outcome was the relationship of ENG level and genomic variants. The funding for the entire study was solely from the Society of Family Planning as outlined in the Disclosure of Funding section (Lines 15-20). No part of this study was funded by or in conjunction with industry.

7) Much of the outcomes measured are from patient self-report. This can be reliable and it can also not be reliable. Are there any data to inform the general reliability of patient recall for the measured bleeding characteristics? I'm reminded of a study that looked at mood and the timing of menses. When the subjects keep a mood diary they found NO association between mood and onset of menses but when the same subjects were given a calendar to recall their mood they consistently recalled being unhappier around the time of their menses. This kind of result makes me nervous about the general reliability of recalled menstrual symptoms.

Thank you for your comment and we agree with your concerns. We are not aware of any published data regarding the reliability of patient recall versus measured bleeding characteristics. We intentionally used a broad question for our primary outcome of "abnormal bleeding" to capture the subjective experience. Available bleeding data demonstrate wide variability in bleeding patterns and similar variability in satisfaction and continuation among women with abnormal or irregular bleeding patterns. Given the constraints of our bleeding question, we incorporated the medical record chart to assess OCP prescription as an objective outcome to support our findings. As increased serum etonogestrel concentrations were associated with both the subjective and objective outcomes, we feel that these results likely reflect a true association with menstrual symptoms.
We added the word "subjective" to the line "To specifically assess subjective bleeding patterns and side effects…" (Lines 121-122) to clarify this point.

8) Line 146 - "Sample size was determined by the primary pharmacogenomic outcome." What? Does this mean the size of this sample was fixed by the other study this was part of OR that the pharmacology features determined the sample size OR something else?

We determined our sample size of 350 women based on the primary outcome of interest (expected change in serum etonogestrel concentrations due to a genetic variant) for our pharmacogenomic publication. We did not perform a separate sample size calculation for the specific outcome of this manuscript (expected increased odds of abnormal bleeding). We have revised this line to make this sentence clearer: "The sample size was determined by the primary pharmacogenomic study size (10)." (Lines 155-156)

9) Line 168 - "Prodrug" Remember the readership…define.

We have removed this term and replaced it with a clear definition. "…containing progestins that are metabolized into or directly related to etonogestrel (e.g. desogestrel)." (Line 169)

10) Lines 210 - 217 - I'm thinking you're trying to point out the irony that if AA women are 2x more likely to have monthly periods, then why are they 4x more likely to get an Rx for OCPs? If that's correct, then make this point a bit more strongly. A control group of non-etonorgetrel users would be nice to see if this sort of race-based menstrual symptoms extends across a different

contraceptive context.

Yes, this is the point that we are trying to make. We have added a line to the end of this paragraph to explicitly remark on this contradiction and your comment regarding the need for investigation of this question with other contraceptive methods.
"Given this unresolved potential contradiction, research on bleeding patterns with other hormonal contraceptive methods may help elucidate the pertinence of our findings." (Lines 227-229)

Overall, pretty simple study that appears to offer new insights into a clinically relevant problem.

Thank you again for your comments and suggestions.

Reviewer #2: Relationship Between Etonogestrel Concentrations and Bleeding Patterns in Contraceptive implant users

This is a cross-sectional sub-study examining women 18-45 years old who have had a contraceptive implant for at least 12 to 36 months. Participants completed a questionnaire regarding bleeding patterns and had a single blood sample drawn for etonogestrel level. The authors hypothesized that increased serum etonogestrel concentrations would increase abnormal or bothersome bleeding with the contraceptive implant.

Materials and Methods

1. Line 112: Were participants compensated for participation?

Yes, participants were compensated a $20 gift card for participation. We have added this to the manuscript. "… and compensated participants with a $20 gift card for their participation." (Lines 116-117)

2. Line 116: It would be helpful to include the questionnaire that patients completed as a supplement.

We have included the pertinent portion of the questionnaire as a supplement (Supplement A) per your suggestion. We reference to this Supplement in Line 121.

3. Line 118: "Abnormal bleeding" is a subjective description. Was a definition provided for participants within the body of the questionnaire?

No, given the subjective nature of abnormal bleeding, we left this question up to the determination of participants as we wanted to capture this subjective experience without biasing participants. This is the primary limitation of our study and we included it as such in the Discussion (Lines 237-243). We have added "subjective" to Line 121-122 as described above to clarify this intention.

4. Line 120-121: How did the authors define monthly period and days of bleeding or spotting over 90-day period? There could be significant overlap with days of bleeding vs. monthly period. Or, were days of bleeding included in the definition with bleeding from menstruation?

In the questionnaire, participants were first asked if they currently experience monthly periods (yes/no). This was again a subjective question that we left up to participants to

determine if they felt that they had regular monthly periods. If the participant responded "no" to having a monthly period, then they were presented with the question about how many days of bleeding or spotting they had over a 90 day period. These responses came directly from the participant, but these two outcomes do not overlap based on the structure of our questionnaire. "We also assessed if participants experienced monthly periods (yes/no) at the time of enrollment, and if not, roughly how many days of bleeding or spotting they had over a 90 day (3 month) period prior to enrollment." (Lines 123-125).

5. Line 121: Why did the authors choose 90 days? Was this derived from the Belsey criteria?

We chose 90 days loosely derived from the Belsey criteria. As this was a retrospective question, we felt that 90 days best balanced the issue of recall bias while providing more pertinent information than a single 30 day period (e.g. able to capture women with irregular but infrequent spotting/bleeding).

6. Lines 145-146: In their related paper Smith et al (2019), the authors conduct a careful power analysis to ensure that their statistical analysis possesses sufficient statistical power. Did the authors conduct a similar analysis for the hypotheses tested in this paper? Is this study adequately powered to detect the outcome of interest? A discussion of this issue would be helpful for readers.

We did not conduct a sample size calculation for the primary hypothesis of this manuscript, as the sample size was determined by the analysis in our prior publication. As we found statistically significant associations relating to our primary hypothesis of this manuscript, we by definition were powered to detect significance for our bleeding outcome of interest. A power analysis is relevant to analysis lacking statistically significant findings, as the lack of significance may be due to lack of power. We do not feel that a power analysis would add to the manuscript, and as such, may actually cause more confusion for readers.

Results:

7. Line 155: The authors report the median serum etonogestrel concentration. It would be helpful to place this in a table for the reader.

We have added the median and range serum etonogestrel concentrations to Table 1.

Discussion:

8. Line 197: Would add a woman is more likely to receive a prescription for management of bothersome bleeding at the Anschutz clinic. This management may not be generalizable to other clinics as other first-line methods include NSAIDs or other hormonal methods.

Thank you for your comment. We have added a line to clarify that prescription of OCPs is first-line treatment for implant related bothersome bleeding at our clinic. "At our clinical setting, first-line treatment for bothersome bleeding with the etonogestrel implant is prescription of oral contraceptive pills." (Lines 202-203)

9. Lines 225-227: The authors conclude the prevalence of bothersome bleeding and overall bleeding patterns are more likely to be representative of the general population of implant users is inaccurate as first-year users are excluded. This should be rephrased.

We apologize for this oversight. We have added a clarification to this line to highlight that

our study population was not representative of implant users prior to 12 months of use. "… population of contraceptive implant users that continue past the first year of use." (Line 239)

10. Line 232-235: The authors obtained confirmatory chart information for only 25% of participants (53 out of 208), which should be specifically clarified in their limitations section.

We apologize for any confusion regarding these numbers as pointed out by Reviewer #1 as well. We had reviewable medical record information for 253 total participants (72.2% of all participants), of whom 53 had documented prescription of OCPs. We have clarified these numbers in the abstract: "Among participants with reviewable medical records (n=253), roughly 20% had received a prescription for oral contraceptive pills during implant use." (Lines 48-49)
We have also added a line to the limitations section of the Discussion to further highlight the exact number of participants who did not have reviewable medical records. "Though 97 participants did not have past medical records available for review, we were able to review records of over 72% of our total participants." (Lines 248-249)

Additional Comments:

11. Readers do not have access to the questionnaire and therefore do not know exactly what "abnormal bleeding" means. Please comment on the decision to ask patients if they had this type of bleeding versus asking participants about the number of days of bleeding.

We have now included the pertinent sections of the questionnaire (Supplement A) to avoid any confusion regarding this question. We have discussed our decision regarding this and its limitations in response to comment #3 above.

12. As the authors mention in the Introduction, per Grunloh et. al, the majority of women who discontinued the implant did so in the first 6 months of use. These data would be valuable for patients and practitioners. Why did the authors choose to not evaluate users in the first year of use?

As this study investigated a pharmacokinetic outcome, we needed participants who were in the relative steady-state period of etonogestrel implant use, which is past the first 12 months of use. We agree that this data would be valuable, but may require different methodology to better handle the pharmacokinetics of implant users in the first year of use. This limitation is included in our Discussion: "Finally, we only enrolled participants with implants past 12 months of use, and thus did not capture early discontinuers of this method who may have different side effect and bleeding profiles." (Lines 249-251).

Reviewer #3: In this cross-sectional study of women using the etonogestrel contraceptive implant presenting for routine contraceptive care or recruited through advertising, those with higher serum etonogestrel levels were found to have higher odds of abnormal bleeding as well as higher odds of treatment for abnormal bleeding.

Introduction

1) line 92-94: is there any basis for the hypothesis that higher etonogestrel concentrations may be associated with abnormal bleeding?

As there are no previous pharmacokinetic studies comparing serum progestin concentrations to bleeding patterns, our hypothesis is based on the higher rates of abnormal bleeding reported with the contraceptive implant compared to lower dose progestin-only methods, such as the levonorgestrel-releasing intrauterine device. However, we were fully prepared for the direction of our hypothesis to be incorrect given the paucity of pre-existing data.

Methods

2) Line 121: the patient survey asked the number of bleeding/spotting days over a 3-month period. Please specify if this meant the last 90 days prior to study enrollment, or some other 90-day period.

This question asked about the last 90 days prior to study enrollment. We have revised this line to clarify this point: "… had over the last 90 day (3 months) period prior to enrollment." (Line 125)

3) Line 127: note that the CDC Selected Practice Recommendations also suggests a trial of NSAIDs for treatment of bothersome bleeding, not just a standard treatment with COCs or estrogen

Thank you for your comment. Although a trial of NSAIDs is a potential treatment for bothersome bleeding with the implant, our clinical setting prescribes OCPs as a first line treatment for bothersome breakthrough bleeding, which is why we looked specifically for this outcome. This is described in Lines 131-133: "We specifically evaluated combined oral contraceptive pill prescription as this is the standard treatment for bothersome breakthrough bleeding with the contraceptive implant at our recruitment sites."

Results

4) Line 151/Table 1: confirm that months of implant use is 25.7 months (per text line 151) vs. 26.0 months (per Table 1)

We apologize for this error. Table 1 is correct and we have fixed this line to state the correct median duration of implant use. "…median duration of etonogestrel implant us of 26.0 months…" (Line 152)

5) Table 1: confirm that median BMI is 25.7 kg/m2, as the 25.7 number is described within the manuscript as the duration of implant use

Table 1 is correct and 25.7 kg/m^2 is the correct median BMI.

6) Table 2: clarify within table caption where there is overlap inn patient self-report of bleeding patterns. For example, are there patients included in the "abnormal bleeding" group who also have a "current monthly period"? The survey questions reflect different timelines, but the data presentation in Table 2 implies mutually exclusive categories.

Thank you for your suggestion. These are not mutually exclusive categories and we have clarified within the caption regarding the overlap between these three categories: "These categories were not mutually exclusive: 91 participants who reported a "current monthly period" also reported ever having "abnormal bleeding" and 14 participants who had "amenorrhea" at the time of enrollment reported ever having "abnormal bleeding"" (Lines 321-324)

7) Table 3: consider presenting regression coefficients for all characteristics and demographic variables of interest that were used in the MLR (age, months of implant use, BMI, race, ethnicity, serum ENG concentration).

We have added a new Table (Table 3) to present the crude odds ratios per your comment and the statistical reviewer's comments.

Discussion

8) Line 194-195: while OR is 1.6 for abnormal bleeding for every 100 pg/mL increase in serum ENG concentration, is this ENG concentration variability likely to be seen in a population? In this study, the IQR of serum ENG concentration is only 63 pg/L, while the majority (59%) experienced abnormal bleeding at some point during their implant use.

Yes, our variability in serum ENG concentrations (12-fold difference between highest and lowest concentrations) is very similar to that found by McNicholas et al (Am J Obstet Gynecol, 2017) and demonstrates that some women will have much higher serum ENG concentrations among a population of contraceptive implant users. Approximately 12.5% of our participants had serum ENG concentrations >100pg/mL greater than participants at the 25th percentile or lower. Many of these 43 participants actually had serum concentrations 200-300pg/mL higher. There is actually a statistically significant increase in the OR for every 1pg/mL increase in serum ENG concentration (Lines 177-180), but we felt this OR was more difficult for readers to interpret than the OR for each 100pg/mL increase.

9) Add comments on how this paper relates to your similar paper on patient characteristics & serum ENG concentration that published in the April Contraception journal.

That paper focused on the significant associations of BMI and duration of implant use on serum ENG concentrations. Those findings remained significant in our pharmacogenomic analysis published in Obstetrics and Gynecology. We have added a line to the discussion to relate the findings of that paper to our findings here: "Though higher BMI and longer duration of implant use are associated with small decreases in serum etonogestrel concentrations, we did not find that these two patient characteristics were associated with bothersome bleeding side effects (17)." (Lines 206-208)

STATISTICAL EDITOR'S COMMENTS:

1. lines 53-55: See later comments re: use of the aORs, but for this sentence, the model actually predicts increase in odds, not 1.6 times more likely, but 1.6x the odds.

We have revised this line to reflect the more accurate language: "…contraceptive implant users in this study had 1.6 times the odds of reporting abnormal bleeding and 2.3 times the odds of having received a prescription as treatment for bothersome bleeding." (Lines 53-54)
We have also revised the manuscript to replace interpretations of these associations as "more likely" to reflect more accurately the increase in odds:
Line 178-180 "…participants had 1.005 times the odds of having experienced abnormal bleeding and 1.008 times the odds of having received a prescription for oral contraceptive pills for bothersome bleeding"
Lines 184-186 "…participants had 0.95 times the odds of having received a prescription for oral contraceptive pills, but participants who self-reported as Black or African American

had 4.5 times the odds of having been prescribed…"
Lines 200-201 "…woman had 1.6 times the odds of reporting having experienced abnormal bleeding and 2.3 times the odds of having received a prescription…"
Lines 216-217 "…Asian or Pacific Islander had over 3 times increased odds of reporting amenorrhea as…"
Lines 220-223 "…participants had over 2 times the odds of reportingwere over 2 times as likely to report current monthly periods. However, it remains unclear from our findings why participants who self-reported as Black or African American had over 4 times the odds of having received a prescription for oral contraceptive pills."

2. lines 155-156: The distribution of serum etonogestrel appears skewed. Did the Authors attempt to normalize the distribution by transforming the data, eg, log or other methods? The relationship with the outcomes may not depend on the serum concentration linearly.

As logistic regression does not rely upon a linear relationship between dependent and independent variables, we did not feel that attempting to normalize serum etonogestrel concentrations was needed. Additional, Changyong et al (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4120293/) has demonstrated that log transformation does not always result in normalized distribution. Therefore, we chose to keep serum etonogestrel concentrations as is.

3. lines 169-187: Need to show more analysis of the relationship between level of circulating progestin and (1) BMI, (2) time since implant and (3) race/ethnicity. Did the racial groups have statistically equivalent time since implant and BMIs? Or, did the level of progestin decrease as the time since implant increased? Similarly, did the progestin level vary inversely with the woman's BMI? Were the follow-up times equivalent for strata based on race? The occurrence of abnormal bleeding or of amenorrhea might be time-dependent, that is, if the follow-up were longer for a particular group, then there would be more time for that side effect/bleeding pattern to manifest. If in fact there were differences in timing, then hazard rate ratios would be the appropriate stats test.

We have previously published the analysis of the relationship between serum ENG concentrations and BMI, duration of implant use, and race/ethnicity (Lazorwitz et al, Contraception 2019; Lazorwitz et al, Obstet Gynecol 2019). Higher BMI and longer duration of use are associated with small decreases in serum ENG concentrations. As these results have already been published, we did not include that analysis in this manuscript. We included duration of use in every multivariable logistic regression model, and so the associations we found are independent of time since implant insertion.
The racial/ethnic groups did not have statistically different median durations of implant use or BMIs (Independent medians test).
Duration of implant use was statistically associated with having received a prescription for oral contraceptive pills (Lines 183-184), but was not associated with abnormal bleeding, amenorrhea, or monthly periods.

4. Table 3: Should include crude ORs to contrast with the aORs. Need to include more of crude ORs/aoRs in terms of serum etonogestrel concentration vs BMI, time since implant, race etc (which could be a separate Table, if desired.) The aORs need further explanation of their referents. For example, the aOR for abn bleeding was 1.005, but that is per 1 pg/mL. That is a perfectly valid metric for the model, but not very useful clinically, since the logistic model increase would be multiplicative per each 1 pg/mL. Instead, the reference in the Abstract seems more clinically useful. That is, for each 100pg/mL increase in serum estonogestrel concentration, the adjusted

odds of abnormal bleeding increased 1.6 x (then insert CIs), which I believe from the Table would be [1.1,2.2]. Similarly for likelihood of a Rx the aOR per 100 pg/mL would be 2.2 [1.3,3.6]. Also, need to show the referent for the duration, which I believe was per month beyond 12 months (the lower range of the distribution).

We have added an additional Table (Table 3) for the crude ORs of all variables of interest. Previous Table 3 is now Table 4. For Table 4, we have changed the serum ENG concentration variable to per 100pg/mL as you suggested. We have placed in the corresponding aOR and 95% CI's for these revised variables. We also added a legend for this Table to show the referent for duration of implant use.

5. Since there were 350 women altogether and of those 40 were Black of African American and among the 350, only about 20% receive oral contraception, the number of Black women receiving OC is likely ~ 10. That is too few to allow for multivariable adjustment, due to potential over fitting of the model. Likewise for the entire cohort of 350, only 19 women were Asian or Pacific Islander. That is too few to allow for multivariable adjustment, also. Also, what were the counts for amenorrhea for the Asian and Pacific Islander and for the other racial groups? Since overall there were 52 instances of amenorrhea (15%), I suspect the counts were low for that racial group and again, the model is over fitted.

The denominator for the OCP analysis was the 253 participants who had medical records available to review. Among participants with medical records available to review for OCP prescription, 28 self-reported as Black and 14 (50%) of these participants received an OCP prescription, as compared to only 17.3% of participants from all other race/ethnicity categories. This is both a statistically and clinically significant difference (Fisher's Exact test, p<0.001) and we do not believe that the model is over fitted.
Among participants who self-reported as Asian or Pacific Islander, 6 (35.3%) reported amenorrhea as compared to 14.4% of all other participants. We again believe that this is a statistically and clinically significant difference (Fisher's Exact test, p=0.03) and that the model is not over fitted.

EDITORIAL OFFICE COMMENTS:

1. The Editors of Obstetrics & Gynecology are seeking to increase transparency around its peer-review process, in line with efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online. Additionally, unless you choose to opt out, we will also be including your point-by-point response to the revision letter, 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:
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2. As of December 17, 2018, Obstetrics & Gynecology has implemented an "electronic Copyright Transfer Agreement" (eCTA) and will no longer be collecting author agreement forms. When you are ready to revise your manuscript, you will be prompted in Editorial Manager (EM) to click on

"Revise Submission." Doing so will launch the resubmission process, and you will be walked through the various questions that comprise the eCTA. Each of your coauthors will receive an email from the system requesting that they review and electronically sign the eCTA.

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.

3. Clinical trials submitted to the journal as of July 1, 2018, must include a data sharing statement. The statement should indicate 1) whether individual deidentified participant data (including data dictionaries) will be shared; 2) what data in particular will be shared; 3) whether additional, related documents will be available (eg, study protocol, statistical analysis plan, etc.); 4) when the data will become available and for how long; and 5) by what access criteria data will be shared (including with whom, for what types of analyses, and by what mechanism). Responses to the five bullet points should be provided in a box at the end of the Methods section.

As this study does not meet the NIH standard definition of a clinical trial, we will not be sharing data at this time.

4. All submissions that are considered for potential publication are run through CrossCheck for originality. The following lines of text match too closely to previously published works. Variance is needed in the following sections:

a. Lines 90-2 ("The etonogestrel contraceptive…of protocol adherence.")

We have revised this line to now state: "Etonogestrel contraceptive implant users are ideal candidates for pharmacokinetic variability studies as they achieve relative steady-state serum concentrations due to the steady drug release nature of the implant. This avoids any confounding stemming from protocol adherence (4, 14)." (Lines 90-92)

b. Lines 97-98 ("In this cross-sectional…with abnormal metabolism." Please also note that these methods have been described before- https://www.sciencedirect.com/science/article/pii/S0010782419301234?via%3Dihub

We have revised these lines and added reference to the published methods from the primary pharmacogenomics publications. These lines now state: "The underlying methodology for this study has previously been published, including all inclusion and exclusion criteria (10). Participants were English or Spanish speaking reproductive age women (18-45 years old) with an etonogestrel contraceptive implant in place for at least 12 and no more than 36 months. Women had to have an implant in place for at least 12 months in order to be in the relative steady-state period of the implant's pharmacokinetics (14)." (Lines 97-102)

c. Lines 129-137 ("We also collected a single….250, and 350 participants").

We have revised these lines to now state: "We performed serum etonogestrel concentration analysis using the previously published methodology that utilized a previously validated liquid chromatography-mass-spectrometry (LCMS) assay protocol (10, 16). All LCMS procedures were performed at the Biomarkers Core Laboratory of the Irving Institute of Clinical and Translational Research at Columbia University Medical Center (New York City, NY)." (Lines 134-138)

5. 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.

The terms used throughout this manuscript come directly from the survey we used to assess bleeding patterns and symptoms and we feel best reflects the subjective responses from our participants. Additionally, the term "normal uterine bleeding" does not fully capture the physiology of women who have a "monthly bleed or period" with a progestin-only contraceptive like the implant. These may be anovulatory cycles and the term "normal uterine bleeding" implies regular cycles with strict definitions on the amount of acceptable variance in length, information which this study did not collect. We also feel that "breakthrough bleeding" is a term used throughout this manuscript not on the reVITALize list that encapsulates some of the physiology of abnormal uterine bleeding with the contraceptive implant and is an important side effect with use of any progestin-only medication.

6. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Original Research reports should not exceed 22 typed, double-spaced pages (5,500 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, tables, boxes, figure legends, and print appendixes) but exclude references.

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

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* 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).

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11. 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.

12. 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.

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