

**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)\*

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: <a href="mailto:obgyn@greenjournal.org">obgyn@greenjournal.org</a>.

<sup>\*</sup>The corresponding author has opted to make this information publicly available.

**Date:** Jan 06, 2020

**To:** "Jugnu Biba Nijjar"

From: "The Green Journal" em@greenjournal.org

Subject: Your Submission ONG-19-2147

RE: Manuscript Number ONG-19-2147

The association of immediate postpartum etonogestrel implant insertion and venous thromboembolism.

### Dear Dr. Nijjar:

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 14 days from the date of this letter. If we have not heard from you by Jan 20, 2020, we will assume you wish to withdraw the manuscript from further consideration.

### **REVIEWER COMMENTS:**

Reviewer #1: This appears to be a retrospective cohort study looking at odds of VTE within 30 days of delivery in women who received immediate postpartum contraceptive implant vs. those who did not. The authors point out the importance of postpartum contraception provided while still in the hospital after delivery. Knowing the potential association between the contraceptive implant placed immediately postpartum and VTE is therefore important information. I do think this is an important study, but would need to be cleaned up a fair amount.

- -In your abstract and throughout paper, would consider using standard immediate postpartum LARC language. Also, not sure I've ever seen the acronym ECI (which you only used in your abstract, I'm assuming to keep the word count down).
- -The introduction states "eliminating immediate postpartum insertion of the etonogestrel implant reduces options..."-- do you believe this would happen just due to the package insert?
- -You state your objective is to estimate risk, but then you calculated odds ratios. While the two may estimate one another with rarer diseases, they are different.
- -Other variables that would have been helpful to look at: other contraceptive use within non-implant group, BMI.
- -For the demographics you did look at, does hypertension include chronic, gestational, pre-eclampsia, etc? Does diabetes include pre and gestational? I know you have codes listed, but a description is more helpful.
- -Does your outcome variable of VTE include PE or just DVT?
- -Would be nice to have your outcome variable in a table rather than just in text to make it easier to find.
- -Discussion: your first paragraph for your outcome statement as well as last paragraph again discusses risk (see above). Also, you only looked at those who were re-admitted with VTE, so your outcome statement should read among those who were re-admitted (you are making too strong of a statement).

Reviewer #2: In this paper, the authors compare the rate of VTE within 30 days of discharge between women with and without etonogestrel contraceptive implant insertion immediate postpartum. Currently the manufacturer of the implant

1/14/2020, 9:34 AM

recommends delaying insertion until 21 days postpartum due to increased VTE risk. This does not match CDC guidelines and this recommendation could limit women from leaving the hospital postpartum with very effective contraception. The authors report no previously published research assessing the association of immediate postpartum implant insertion and VTE. This study has the potential to close a gap in the research. I have a few comments about the study as presented which are as follows

#### Abstract:

- 1. Clear concise summary of their study.
- 2. In sentences 58 I do not think you need "or had" between smoker, hypertension. I like the phrasing from the results better "More women who had ECI placement"
- 3. In sentence 63 "Immediately" can be changed to "immediate". I would use same language through out.

#### Introduction:

1. The introduction does a great job setting up your objectives and importance of this study.

## Methods:

- 1. This may go without saying but was the data used from Jan 1 2016 Dec 31 2016. It sounds like it was one year of data but I would be specific.
- 2. Did the database not include information on BMI? Other progestin contraception (depo or IUDs started prior to discharge)?
- 3. I noticed you did not include a search code for the device. This may be a good way to double check you are not missing some implant insertions (billing for the device is more important as reimbursement for the device is higher than for insertion).
- 4. I think your statistical methods are sound.

#### Results:

- 1. Your average age for implant users in the text does not meet the age listed in Table 1.
- 2. In the abstract you listed Medicaid but in the results you grouped this as "government sponsored insurance" (which looks like it is Medicaid and Medicare). I would define this team if you are going to group them and keep it consistent through out the paper.

#### Discussion:

- 1. I would include come discussion of why the majority of women getting immediate postpartum implant insertion had government sponsored insurance. My guess is that in many states this is the only insurance who currently will reimburse for this. This makes your implant population inherently different (some would say at higher baseline risk of VTE due to other associated factors).
- 2. Do you have a plausible hypothesis why VTE risk would differ between immediate postpartum depo and implant use? If you do I would include this in the conclusion.
- 3. Another limitation may be other hormonal contraception not included in the analysis. Many women may start combined hormones at 21 days postpartum or have left the hospital with other progestin only methods not included. This could affect your baseline VTE risk.

### Figures/Tables:

1. Figure 1 - Did not include the IDC 10 codes used to search for implant insertion. I would include all codes used

Reviewer #3: The authors present a well written database study of the risk of VTE in patients receiving LARC therapy. This is an important topic and germane one given the number of women who receive LARCs in 2019. Overall this was a well written paper without being over reaching and I think has a good change of being cited well.

### Specific comments:

- 1) The introduction is a bit sparse and should be expounded upon. Perhaps add some data on efficacy of LARC therapy and baseline risk of VTE in the postpartum period
- 2) Lines 98-100: I do have some concern about abstracting data from these diagnosis codes as these are notoriously unreliable. How did the authors validate this?
- 3) Line 125: it is interesting that more women had HTN that got an IUD; what is the hypothesis behind this
- 4) The results section is also a bit sparse. There is clearly other data that could be reported that help validate your claim such as inclusion of other parameters into your univariate and multivariate model
- 5) The authors should expand on the weaknesses of large database studies as well. It is nice however to see a database study which does not show an association given that the large numbers analyzed almost always show an association.

2 of 6 1/14/2020, 9:34 AM

### STATISTICAL EDITOR COMMENTS:

The Statistical Editor makes the following points that need to be addressed:

lines 54-55 and elsewhere: Need to include the 95% CIs for the estimates of incidence, which are quite wide for the ECI cohort, owing to the number of events (7) in that cohort. IR = 0.8/1000, CI 0.3 to 1.7 per 1000, while for the control group IR = 0.35/1000, with CI = 0.33 to 0.37 per 1000.

lines 118-132: The study was negative, but also under powered. Given the incidence rates and relative sizes of the control vs ECI cases, the statistical power to have discerned the difference was ~ 60%. Put another way, using the proportions cited and relative sizes of the samples, it would require about 2x the sample of both cases and controls to establish no statistical difference with the usual power of 80%. The samples are large, but the rate limiting number is the event count in the ECI cohort. Put another way, it takes very large samples to establish NS difference when the frequency of adverse events is small. In part, this can be inferred from the wide CIs of the OR.

lines 129-132: Another issue is the adjustment for baseline differences, given the limited number of adverse events among the ECI cohort vs adjustment for 6 variables. A better approach might have been to match the ECI cohort to a subset of the control group, but then the insufficient power issue would have been exacerbated.

### **EDITOR COMMENTS:**

General: In your revision to a descriptive study, please address the statistical editor's comment "Put another way, using the proportions cited and relative sizes of the samples, it would require about 2x the sample of both cases and controls to establish no statistical difference with the usual power of 80%. The samples are large, but the rate limiting number is the event count in the ECI cohort. Put another way, it takes very large samples to establish NS difference when the frequency of adverse events is small. In part, this can be inferred from the wide CIs of the OR" by including the number needed to study to attain adequate power to support your conclusion that the immediate insertion of the device does not increase the risk for VTE.

1. We no longer require that authors adhere to the Green Journal format with the first submission of their papers. However, any revisions must do so. I strongly encourage you to read the instructions for authors (the general bits as well as those specific to the feature-type you are submitting). The instructions provide guidance regarding formatting, word and reference limits, authorship issues, and other things. Adherence to these requirements with your revision will avoid delays during the revision process, as well as avoid re-revisions on your part in order to comply with the formatting. For instance, the abstract objective should be a simple "To" statement without background.

Line 57: I'm uncertain what you are saying in this sentence. Were women who underwent ECI Placement more likely to be smokers, hypertensive, etc? You say they "were younger" but thereafter there is no comparison given.

Line 59: It is an idiosyncratic fact that at the Journal we tend to avoid the use of the word impact to imply the result of a change, preferring to limit "impact" to mean a physical blow. As well, this sentence implies causation. Please avoid causal language throughout your manuscript. Your study can identify and quantify associations, but not causation. Language should be changed in the precis, abstract, and manuscript, if causal language is used in those sites.

Line 76: Please provide the full name for the CDC.

Line 92: Perhaps "It includes roughly 36 million discharges annually....."

Line 94: Please see the following article and consider it's recommendations.

September 25, 2019

The Use of the International Classification of Diseases, Tenth Revision, Clinical Modification and Procedure Classification System in Clinical and Health Services ResearchThe Devil Is in the Details

Garth H. Utter, MD, MSc1,2; Oluseun O. Atolagbe, MBBS, MPH, CCS3; David T. Cooke, MD1,2

**Author Affiliations** 

JAMA Surg. 2019;154(12):1089-1090. doi:10.1001/jamasurg.2019.2899

Full Text

In October 2015, the US Department of Health and Human Services began requiring hospitals and other entities to use the International Classification of Diseases, Tenth Revision, Clinical Modification and Procedure Classification System (ICD-10-CM/PCS). Datasets commonly used for clinical and health services research are now starting to incorporate the ICD-10-

3 of 6 1/14/2020, 9:34 AM

CM/PCS diagnosis and procedure codes. Researchers must grapple with these entirely new and markedly more elaborate classifications, and journal reviewers, editors, and readers will need to consider the methodologic quality of studies based on the ICD-10-CM/PCS. Although recent articles addressed some considerations involved in this shift to the ICD-10-CM/PCS,1,2 they did not squarely focus on its application to surgical research, adjuncts, and associated optimal practices.

Line 118: perhaps "during which, 8,369 women received...."?

### Results section:

Data on lines 120 and 121 are presented as raw numbers without comparisons, but it is written as if there are statistical differences. Please provide the comparisons.

### P Values vs Effect Size and Confidence Intervals

While P values are a central part of inference testing in statistics, when cited alone, often the strength of the conclusion can be misunderstood. Whenever possible, the preferred citation should be in terms of an effect size, such as odds ratio or relative risk or the mean difference of a variable between two groups, expressed with appropriate confidence intervals. When such syntax is used, the P value has only secondary importance and often can be omitted or noted as footnotes in a Table format. Putting the results in the form of an effect size makes the result of the statistical test more clinically relevant and gives better context than citing P values alone.

This is true for the abstract as well as the manuscript, tables and figures.

Please provide absolute values for variables, in addition to assessment of statistical significance. We ask that you provide crude OR or RR's followed by adjusted values for all variables.

Line 135: Discussion. Please note the limitations here described the statistical editor. As you are underpowered to conclude the lack of difference, you should temper your conclusions. You can certainly talk about how reassuring it is that the rates of VTE in the ECI group is low, but you really cannot conclude that you showed no difference.

Line 139: Avoid duplicating information in the introduction and the discussion. Also (line 135) avoid single sentence paragraphs.

## **EDITORIAL OFFICE COMMENTS:**

- 1. The Editors of Obstetrics & Gynecology are seeking to increase transparency around its peer-review process, in line with efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online. Additionally, unless you choose to opt out, we will also be including your point-by-point response to the revision letter. If you opt out of including your response, only the revision letter will be posted. Please reply to this letter with one of two responses:
- A. OPT-IN: Yes, please publish my point-by-point response letter.
- B. OPT-OUT: No, please do not publish my point-by-point response letter.
- 2. As of December 17, 2018, Obstetrics & Gynecology has implemented an "electronic Copyright Transfer Agreement" (eCTA) and will no longer be collecting author agreement forms. When you are ready to revise your manuscript, you will be prompted in Editorial Manager (EM) to click on "Revise Submission." Doing so will launch the resubmission process, and you will be walked through the various questions that comprise the eCTA. Each of your coauthors will receive an email from the system requesting that they review and electronically sign the eCTA.

Please check with your coauthors to confirm that the disclosures listed in their eCTA forms are correctly disclosed on the manuscript's title page.

- 3. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions. Please access the obstetric and gynecology data definitions at https://www.acog.org/About-ACOG/ACOG-Departments/Patient-Safety-and-Quality-Improvement/reVITALize. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.
- 4. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: 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, references, tables, boxes, figure legends, and print appendixes) but exclude references.
- 5. Specific rules govern the use of acknowledgments in the journal. Please note the following guidelines:

4 of 6 1/14/2020, 9:34 AM

- \* All financial support of the study must be acknowledged.
- \* Any and all manuscript preparation assistance, including but not limited to topic development, data collection, analysis, writing, or editorial assistance, must be disclosed in the acknowledgments. Such acknowledgments must identify the entities that provided and paid for this assistance, whether directly or indirectly.
- \* All persons who contributed to the work reported in the manuscript, but not sufficiently to be authors, must be acknowledged. Written permission must be obtained from all individuals named in the acknowledgments, as readers may infer their endorsement of the data and conclusions. Please note that your response in the journal's electronic author form verifies that permission has been obtained from all named persons.
- \* If all or part of the paper was presented at the Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists or at any other organizational meeting, that presentation should be noted (include the exact dates and location of the meeting).
- 6. 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.

- 7. Only standard abbreviations and acronyms are allowed. A selected list is available online at http://edmgr.ovid.com/ong/accounts/abbreviations.pdf. Abbreviations and acronyms cannot be used in the title or précis. Abbreviations and acronyms must be spelled out the first time they are used in the abstract and again in the body of the manuscript.
- 8. The journal does not use the virgule symbol (/) in sentences with words. Please rephrase your text to avoid using "and/or," or similar constructions throughout the text. You may retain this symbol if you are using it to express data or a measurement.
- 9. In your Abstract, manuscript Results sections, and tables, the preferred citation should be in terms of an effect size, such as odds ratio or relative risk or the mean difference of a variable between two groups, expressed with appropriate confidence intervals. When such syntax is used, the P value has only secondary importance and often can be omitted or noted as footnotes in a Table format. Putting the results in the form of an effect size makes the result of the statistical test more clinically relevant and gives better context than citing P values alone.

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

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

- 10. 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.
- 11. 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.
- 12. 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.

- 13. If you choose to revise your manuscript, please submit your revision through Editorial Manager at http://ong.editorialmanager.com. Your manuscript should be uploaded in a word processing format such as Microsoft Word. Your revision's cover letter should include the following:
  - $^st$  A confirmation that you have read the Instructions for Authors (http://edmgr.ovid.com/ong/accounts/authors.pdf),

5 of 6 1/14/2020, 9:34 AM

and

\* A point-by-point response to each of the received comments in this letter.

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

Again, your paper will be maintained in active status for 14 days from the date of this letter. If we have not heard from you by Jan 20, 2020, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Nancy C. Chescheir, MD Editor-in-Chief

2018 IMPACT FACTOR: 4.965

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

In compliance with data protection regulations, you may request that we remove your personal registration details at any time. (Use the following URL: https://www.editorialmanager.com/ong/login.asp?a=r). Please contact the publication office if you have any questions.

6 of 6 1/14/2020, 9:34 AM

**Date:** Jan 15, 2020

To: "Jugnu Biba Nijjar"

From: "The Green Journal" em@greenjournal.org

Subject: Your Submission ONG-19-2147R1

RE: Manuscript Number ONG-19-2147R1

The association of immediate postpartum etonogestrel implant insertion and venous thromboembolism.

Dear Dr. Nijjar:

Your revised manuscript has been reviewed by the handling Editor. Before a final decision can be made, we need you to address the following comments. Please make the requested changes to the latest version of your manuscript that is uploaded to your Author account in Editorial Manager (1-15-20v2). Please contact me by email if you cannot locate this file.

Please track your changes and leave the ones made by the Editorial Office. Your next version should be uploaded to Editorial Manager with a point-by-point reply letter to the comments below.

Your next version will be due by January 29.

- 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. Per journal style, you may list a maximum of 2 degrees here. Please remove one of your degrees here in the byline and below in your Corresponding Author information.
- 3. If your paper is accepted for the Green Journal, we'll schedule it for our June issue until you let us know whether it's accepted for the 2020 ACOG ACSM.
- 4. Line 59: This should read "There was no difference identified in the rate of readmission for VTE between exposed and unexposed women. Of these, 7.......
- 5. Line 65: I'm uncertain what sentence on Line 66 means. What does 'more women....were younger" mean? Younger than what? Or do you mean, "Women that underwent contraceptive implant placement were younger and were more likely to have government-sponsored health insurance, to have smoked, and to have had hypertension than...."
- 6. Line 69: This sentence should read something like "After adjusting for these confounders, there remained no difference in rates of VTE....."
- 7. Line 71: Your results show no difference and are underpowered to do so. Therefore, you cannot conclude that the rate in exposed is "low" compared to women without the placement You can conclude that you did not show an increased risk of VTE in exposed women, but were underpowered to show a protective effect.
- 8. Line 92: Sorry to just be catching this on this edit: This is known as a primacy claim: yours is the first, biggest, best study of its kind. In order to make such a claim, please provide the databases you have searched (PubMed, Google Scholar, EMBASE for example), the dates of your search, and the search terms used. If not done, please edit it out of the paper.
- 9. Line 153: Edit from, "Of women readmitted....", as recommended in the abstract comments.
- 10. Line 164: As with the comments in the abstract section, please edit the discussion section to reflect the inability to note a difference in the two groups. It's terrific that there is not an increase—you just cannot show a protective effect.
- 11. Line 172: Again, you need to talk about underpowered characteristic for detecting a protective effect.
- 12. Line 195: It would be balanced to add that there is some concern that women receiving Medicaid insurance are disproportionately encouraged to use LARC due to systematic bias.

Best, Randi Zung

1 of 2 1/17/2020, 10:21 AM

Editorial Administrator for Dr. Chescheir

In compliance with data protection regulations, you may request that we remove your personal registration details at any time. (Use the following URL: https://www.editorialmanager.com/ong/login.asp?a=r). Please contact the publication office if you have any questions.

2 of 2

January 13, 2020

Editor

Obstetrics & Gynecology

RE: Manuscript ID ONG-19-2147

Dear Editor,

We wish to thank the Editors and Reviewers for their comments. We also want to thank you for the opportunity to do the revisions. The suggestions were fantastic, and the manuscript is stronger from them. We will address each comment individually. We have attached a manuscript version with the Track Changes as well as a "clean version" with the Track Changes accepted for ease of readability. The line numbers refer to the revised Track Changes version. Each author has approved the final form of the revision. Regarding the inquiry of transparency around peerreview, yes, please publish our point-by-point response letter (OPT-IN). This letter serves as confirmation we have read the Instructions for Authors for this article type (i.e. Original Research). Finally, we have followed in the document the STROBE guideline for cohort studies and a checklist has been attached (lines numbers on the checklist are from the Track Changes version). Our institution has deemed this study exempt from IRB approval and we have attached a letter from our institution's IRB stating this.

Best regards,

Biba Nijjar, MD

### **REVIEWER COMMENTS:**

## Reviewer #1:

This appears to be a retrospective cohort study looking at odds of VTE within 30 days of delivery in women who received immediate postpartum contraceptive implant vs. those who did not. The authors point out the importance of postpartum contraception provided while still in the hospital after delivery. Knowing the potential association between the contraceptive implant placed immediately postpartum and VTE is therefore important information. I do think this is an important study, but would need to be cleaned up a fair amount.

-In your abstract and throughout paper, would consider using standard immediate postpartum LARC language. Also, not sure I've ever seen the acronym ECI (which you only used in your abstract, I'm assuming to keep the word count down).

We do use the terminology of "LARC" in the Introduction. However, as part of the reVITALize data definitions, LARC includes both IUD and subdermal implants. So we opted to be more specific with the term of etonogestrel contraceptive implant. We have dropped utilizing the acronym "ECI" since this was not a standard acronym or part of the reVITALize data definitions from ACOG.

-The introduction states "eliminating immediate postpartum insertion of the etonogestrel implant reduces options..."-- do you believe this would happen just due to the package insert?

We have deleted these lines in the Abstract. We do have a statement in the Discussion (lines 194 to 196) that indicate "...the manufacturer recommended delay of etonogestrel contraceptive implant insertion until 21 days postpartum *might* reduce immediate placement secondary to physician and patient concerns." We have already begun seeing practitioners at our hospital doing this.

-You state your objective is to estimate risk, but then you calculated odds ratios. While the two may estimate one another with rarer diseases, they are different.

We have changed the wording in the objective from "risk" to "rate." Since we adjusted for potential confounding variables, OR were utilized.

-Other variables that would have been helpful to look at: other contraceptive use within non-implant group, BMI.

We agree, unfortunately the NRD dataset does not have this available.

-For the demographics you did look at, does hypertension include chronic, gestational, preeclampsia, etc? Does diabetes include pre and gestational? I know you have codes listed, but a description is more helpful.

Yes, we did include all of these conditions. We have added this to the legend of Table 1.

-Does your outcome variable of VTE include PE or just DVT?

Yes, we did group these together. We have defined this in the Method section, lines 132 to 133 and added this to the legend in Table 1.

-Would be nice to have your outcome variable in a table rather than just in text to make it easier to find.

While we appreciate this suggestion, it would be very difficult to add to Table 2.

-Discussion: your first paragraph for your outcome statement as well as last paragraph again discusses risk (see above). Also, you only looked at those who were re-admitted with VTE, so your outcome statement should read among those who were re-admitted (you are making too strong of a statement).

We have changed the language on lines 170 and 237.

## Reviewer #2:

In this paper, the authors compare the rate of VTE within 30 days of discharge between women with and without etonogestrel contraceptive implant insertion immediate postpartum. Currently the manufacturer of the implant recommends delaying insertion until 21 days postpartum due to

increased VTE risk. This does not match CDC guidelines and this recommendation could limit women from leaving the hospital postpartum with very effective contraception. The authors report no previously published research assessing the association of immediate postpartum implant insertion and VTE. This study has the potential to close a gap in the research. I have a few comments about the study as presented which are as follows

## Abstract:

1. Clear concise summary of their study.

# Thank you.

2. In sentences 58 - I do not think you need "or had" between smoker, hypertension. I like the phrasing from the results better "More women who had ECI placement"

These edits have been added.

3. In sentence 63 - "Immediately" can be changed to "immediate". I would use same language through out.

These edits have been added.

## Introduction:

1. The introduction does a great job setting up your objectives and importance of this study.

## Thank you.

## Methods:

1. This may go without saying but was the data used from Jan 1 2016 - Dec 31 2016. It sounds like it was one year of data but I would be specific.

We have clarified the time frame of when the data is collected in lines 108 to 111.

2. Did the database not include information on BMI? Other progestin contraception (depo or IUDs started prior to discharge)?

The dataset does not contain patient BMI. We did not exclude women receiving depot medroxyprogesterone initiation prior to hospital discharge. While there is a procedure code for insertion of the IUD, it does not differentiate between the Copper versus progesterone-coated device. We did add a statement in the Discussion section (lines 233 to 237) listing this limitation.

3. I noticed you did not include a search code for the device. This may be a good way to double check you are not missing some implant insertions (billing for the device is more important as reimbursement for the device is higher than for insertion).

We thank the Reviewer for noting this. We did use the procedure code for subdermal implant insertion. We have added this to Table 1.

4. I think your statistical methods are sound.

Thank you.

## Results:

1. Your average age for implant users in the text does not meet the age listed in Table 1.

Thank you for pointing this out. We have corrected the text.

2. In the abstract you listed Medicaid but in the results you grouped this as "government sponsored insurance" (which looks like it is Medicaid and Medicare). I would define this team if you are going to group them and keep it consistent through out the paper.

This has been defined and made consistent in the document.

### Discussion:

1. I would include come discussion of why the majority of women getting immediate postpartum implant insertion had government sponsored insurance. My guess is that in many states this is the only insurance who currently will reimburse for this. This makes your implant population inherently different (some would say at higher baseline risk of VTE due to other associated factors).

We have added lines in the Discussion, lines 209 to 214.

2. Do you have a plausible hypothesis why VTE risk would differ between immediate postpartum depo and implant use? If you do I would include this in the conclusion.

We agree with the Reviewer that a plausible hypothesis would be fascinating. It would be speculative at best. However, we do have a statement on lines 192 to 193 to this effect and have added the word "thrombogenic" effect.

3. Another limitation may be other hormonal contraception not included in the analysis. Many women may start combined hormones at 21 days postpartum or have left the hospital with other progestin only methods not included. This could affect your baseline VTE risk.

We have added this limitation in the Discussion section (lines 233 to 237).

## Figures/Tables:

1. Figure 1 - Did not include the IDC 10 codes used to search for implant insertion. I would include all codes used

We have added these codes to Table 1.

### Reviewer #3:

The authors present a well written database study of the risk of VTE in patients receiving LARC therapy. This is an important topic and germane one given the number of women who receive

LARCs in 2019. Overall this was a well written paper without being over reaching and I think has a good change of being cited well.

# Specific comments:

1) The introduction is a bit sparse and should be expounded upon. Perhaps add some data on efficacy of LARC therapy and baseline risk of VTE in the postpartum period

While we appreciate this suggestion, we are limited by the journal's requirements of limiting the Introduction to 250 words (we are at 254 already). In addition, the journal's instructions for authors recommends to avoid a detailed literature review in this section.

2) Lines 98-100: I do have some concern about abstracting data from these diagnosis codes as these are notoriously unreliable. How did the authors validate this?

We have clarified this in the Methods section in lines 115 to 120.

3) Line 125: it is interesting that more women had HTN that got an IUD; what is the hypothesis behind this

No patients received an IUD in our cohort. However, more women that received the subdermal implant had hypertension. We speculate that physicians are more comfortable prescribing a progesterone-based contraceptive to women with hypertension. However, our analysis from this dataset would not be able to answer the hypothesis behind this. We did however, do multivariable logistic regression which included this variable.

4) The results section is also a bit sparse. There is clearly other data that could be reported that help validate your claim such as inclusion of other parameters into your univariate and multivariate model

We identified all relevant characteristics that we thought could be associated with an increased rate of VTE. However, we have added language to the Discussion section (lines 211 to 214) that a limitation is there may be other variables we are not able to correct for.

5) The authors should expand on the weaknesses of large database studies as well. It is nice however to see a database study which does not show an association given that the large numbers analyzed almost always show an association.

We have added language to the Discussion section and an additional reference (suggested by the Editor) that discusses weaknesses of using datasets based on ICD-10 discharge codes.

## STATISTICAL EDITOR COMMENTS:

The Statistical Editor makes the following points that need to be addressed:

lines 54-55 and elsewhere: Need to include the 95% CIs for the estimates of incidence, which are quite wide for the ECI cohort, owing to the number of events (7) in that cohort. IR = 0.8/1000, CI 0.3 to 1.7 per 1000, while for the control group IR = 0.35/1000, with CI = 0.33 to 0.37 per 1000.

# Thank you for this edit. This has been included.

lines 118-132: The study was negative, but also under powered. Given the incidence rates and relative sizes of the control vs ECI cases, the statistical power to have discerned the difference was ~ 60%. Put another way, using the proportions cited and relative sizes of the samples, it would require about 2x the sample of both cases and controls to establish no statistical difference with the usual power of 80%. The samples are large, but the rate limiting number is the event count in the ECI cohort. Put another way, it takes very large samples to establish NS difference when the frequency of adverse events is small. In part, this can be inferred from the wide CIs of the OR.

Thank you for this suggestion. We have added a post-hoc power analysis and necessary sample size calculation for the usual power of 80% into our Discussion on lines 225 to 228.

lines 129-132: Another issue is the adjustment for baseline differences, given the limited number of adverse events among the ECI cohort vs adjustment for 6 variables. A better approach might have been to match the ECI cohort to a subset of the control group, but then the insufficient power issue would have been exacerbated.

Thank you for this suggestion. However, we do agree with your analysis that due to the rare number of events in the etonogestrel contraceptive implant group, this would have intensified the limitation of power for our study. We therefore did not proceed with this investigation due to this fact.

## **EDITOR COMMENTS:**

General: In your revision to a descriptive study, please address the statistical editor's comment "Put another way, using the proportions cited and relative sizes of the samples, it would require about 2x the sample of both cases and controls to establish no statistical difference with the usual power of 80%. The samples are large, but the rate limiting number is the event count in the ECI cohort. Put another way, it takes very large samples to establish NS difference when the frequency of adverse events is small. In part, this can be inferred from the wide CIs of the OR" by including the number needed to study to attain adequate power to support your conclusion that the immediate insertion of the device does not increase the risk for VTE.

Thank you for this suggestion. We have addressed this concern in the Discussion on lines 221 to 228.

1. We no longer require that authors adhere to the Green Journal format with the first submission of their papers. However, any revisions must do so. I strongly encourage you to read the instructions for authors (the general bits as well as those specific to the feature-type you are submitting). The instructions provide guidance regarding formatting, word and reference limits, authorship issues, and other things. Adherence to these requirements with your revision will avoid delays during the revision process, as well as avoid re-revisions on your part in order to comply with the formatting. For instance, the abstract objective should be a simple "To" statement without background.

We have carefully reviewed the instructions for authors and gone through the manuscript. The corrections have been made.

Line 57: I'm uncertain what you are saying in this sentence. Were women who underwent ECI Placement more likely to be smokers, hypertensive, etc? You say they "were younger" but thereafter there is no comparison given.

Thank you for pointing this out. We have added language to lines 68 to 69 to correct this.

Line 59: It is an idiosyncratic fact that at the Journal we tend to avoid the use of the word impact to imply the result of a change, preferring to limit "impact" to mean a physical blow. As well, this sentence implies causation. Please avoid causal language throughout your manuscript. Your study can identify and quantify associations, but not causation. Language should be changed in the precis, abstract, and manuscript, if causal language is used in those sites.

Thank you for these suggestions. We have removed the word, "impact." We have gone through the entire manuscript and changed any language that implied causality.

Line 76: Please provide the full name for the CDC.

This has been added to line 90.

Line 92: Perhaps "It includes roughly 36 million discharges annually....."

This correction has been made on lines 107 to 108.

Line 94: Please see the following article and consider it's recommendations. September 25, 2019

The Use of the International Classification of Diseases, Tenth Revision, Clinical Modification and Procedure Classification System in Clinical and Health Services ResearchThe Devil Is in the Details Garth H. Utter, MD, MSc1,2; Oluseun O. Atolagbe, MBBS, MPH, CCS3; David T. Cooke, MD1,2 Author Affiliations JAMA Surg. 2019;154(12):1089-1090. doi:10.1001/jamasurg.2019.2899 Full Text In October 2015, the US Department of Health and Human Services began requiring hospitals and other entities to use the International Classification of Diseases, Tenth Revision, Clinical Modification and Procedure Classification System (ICD-10-CM/PCS). Datasets commonly used for clinical and health services research are now starting to incorporate the ICD-10-CM/PCS diagnosis and procedure codes.

Researchers must grapple with these entirely new and markedly more elaborate classifications, and journal reviewers, editors, and readers will need to consider the methodologic quality of studies based on the ICD-10-CM/PCS. Although recent articles addressed some considerations involved in this shift to the ICD-10-CM/PCS,1,2 they did not squarely focus on its application to surgical research, adjuncts, and associated optimal practices.

Thank you so much for sharing this article with us. We actually had employed several of these techniques without describing them. We have now added these important aspects on lines 115 to 120. We have also added this reference and mentioned these limitations on lines 206 to 209.

Line 118: perhaps "during which, 8,369 women received...."?

This edit has been added to line 147. Thank you.

### Results section:

Data on lines 120 and 121 are presented as raw numbers without comparisons, but it is written as if there are statistical differences. Please provide the comparisons.

These comparisons have been added on lines 148 to 159.

P Values vs Effect Size and Confidence Intervals While P values are a central part of inference testing in statistics, when cited alone, often the strength of the conclusion can be misunderstood. Whenever possible, the preferred citation should be in terms of an effect size, such as odds ratio or relative risk or the mean difference of a variable between two groups, expressed with appropriate confidence intervals. When such syntax is used, the P value has only secondary importance and often can be omitted or noted as footnotes in a Table format. Putting the results in the form of an effect size makes the result of the statistical test more clinically relevant and gives better context than citing P values alone. This is true for the abstract as well as the manuscript, tables and figures.

In the Abstract, Results, and Table 2, we have added effect size measures.

Please provide absolute values for variables, in addition to assessment of statistical significance.

We ask that you provide crude OR or RR's followed by adjusted values for all variables.

The absolute values with the assessment of statistical significance has been added to the Results. The crude and adjusted ORs are shown in the Results with confidence intervals.

Line 135: Discussion. Please note the limitations here described the statistical editor. As you are underpowered to conclude the lack of difference, you should temper your conclusions. You can certainly talk about how reassuring it is that the rates of VTE in the ECI group is low, but you really cannot conclude that you showed no difference.

We have added the limitations as suggested by the Statistical Editor. We have tempered our conclusions regarding any statements of no difference.

Line 139: Avoid duplicating information in the introduction and the discussion. Also (line 135) avoid single sentence paragraphs.

Thank you for noting this. We have removed duplicate information.

# **EDITORIAL OFFICE COMMENTS:**

1. The Editors of Obstetrics & Gynecology are seeking to increase transparency around its peer-review process, in line with efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online. Additionally, unless you choose to opt out, we will also be including your point-by-point response to the revision letter. If you opt out of including

your response, only the revision letter will be posted. Please reply to this letter with one of two responses:

- A. OPT-IN: Yes, please publish my point-by-point response letter.
- B. OPT-OUT: No, please do not publish my point-by-point response letter.

We have chosen to opt-in. Yes, please publish our point-by-point response letter.

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

Please check with your coauthors to confirm that the disclosures listed in their eCTA forms are correctly disclosed on the manuscript's title page.

## We have confirmed with our authors their disclosures are correct.

3. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions. Please access the obstetric and gynecology data definitions at <a href="https://urldefense.proofpoint.com/v2/url?u=https-34">https://urldefense.proofpoint.com/v2/url?u=https-34</a> www.acog.org About-2DACOG ACOG-2DDepartments Patient-2DSafety-2Dand-2DQuality-2DImprovement reVITALize&d=DwIGaQ&c=ZQs-KZ80xEw0p81sqgiaRA&r=YRtpIZpx1v68pIHca54vbxrulf5NyF\_FlcjBW\_IE7fk&m=RSrZXsQ1xyU\_MneRUiFheCdlqrjv8F5PW3\_YjGLs9V0&s=0GKX1Jw7DQyfd9g2uFEyFy9tqSqFaUcChrsvbJtfuag&e= . If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

## We have confirmed we are utilizing only approved data definitions.

4. 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, references, tables, boxes, figure legends, and print appendixes) but exclude references.

## We are compliant with the space limitations of the journal.

- 5. Specific rules govern the use of acknowledgments in the journal. Please note the following guidelines:
- \* All financial support of the study must be acknowledged.
- \* Any and all manuscript preparation assistance, including but not limited to topic development, data collection, analysis, writing, or editorial assistance, must be disclosed in the acknowledgments. Such acknowledgments must identify the entities that provided and paid for

this assistance, whether directly or indirectly.

- \* All persons who contributed to the work reported in the manuscript, but not sufficiently to be authors, must be acknowledged. Written permission must be obtained from all individuals named in the acknowledgments, as readers may infer their endorsement of the data and conclusions. Please note that your response in the journal's electronic author form verifies that permission has been obtained from all named persons.
- \* If all or part of the paper was presented at the Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists or at any other organizational meeting, that presentation should be noted (include the exact dates and location of the meeting).

# We are compliant with all of these requirements.

6. 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.

We have confirmed our Abstract is consistent with the main text. Our Abstract is within the word limit and a word count has been provided.

7. Only standard abbreviations and acronyms are allowed. A selected list is available online at <a href="https://urldefense.proofpoint.com/v2/url?u=http-">https://urldefense.proofpoint.com/v2/url?u=http-</a>

3A edmgr.ovid.com ong accounts abbreviations.pdf&d=DwlGaQ&c=ZQs-KZ8oxEw0p81sqgiaRA&r=YRtplZpx1v68plHca54vbxrulf5NyF\_FlcjBW\_lE7fk&m=RSrZXsQ1xyU\_MneRUiFheCdlqrjv8F5PW3\_YjGLs9V0&s=fkOMixuTav0wbqyuiy5MXyxMjo02LJ8elTu87Vzx3i\_0&e= . 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.

We have confirmed we are using only standard acronyms.

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

We have confirmed we are not using the virgule symbol.

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

We have added effect size in the Abstract and Result sections. These P values have been removed.

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

This is not applicable to our manuscript.

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

We have standardized our presentation of data throughout the manuscript with these guidelines in mind.

10. Please review the journal's Table Checklist to make sure that your tables conform to journal style. The Table Checklist is available online here:

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We have confirmed our tables are consistent with the journal's style.

11. 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

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The ACOG documents we cite are the current ones.

12. 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

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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.

We will be monitoring our email.

13. If you choose to revise your manuscript, please submit your revision through Editorial Manager at <a href="https://urldefense.proofpoint.com/v2/url?u=http-">https://urldefense.proofpoint.com/v2/url?u=http-</a>

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<u>KZ8oxEw0p81sqgiaRA&r=YRtplZpx1v68plHca54vbxrulf5NyF\_FlcjBW\_lE7fk&m=RSrZXsQ1xyU\_MneRUiFheCdlqrjv8F5PW3\_YjGLs9V0&s=LEpyKd264pHtlFvKOl0hDNqukFuT5GLHJhX4dN5\_qorw&e=</u>. Your manuscript should be uploaded in a word processing format such as Microsoft Word. Your revision's cover letter should include the following:

\* A confirmation that you have read the Instructions for Authors

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7unzVbLju0f2O9gMhkqSHvWN5GbOq&e= ), and

\* A point-by-point response to each of the received comments in this letter.

We have read the instructions for authors and submitted a point-by-point response.

January 17, 2020

Editor

Obstetrics & Gynecology

RE: Manuscript ID ONG-19-2147R1

Dear Editor,

Thank you so much again to have the opportunity for further edits on our manuscript. We have attached a manuscript version with the Track Changes. The line numbers in the responses below refer to the revised Track Change version.

Best regards,

Biba Nijjar, MD

- 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. We have reviewed all the edits to the manuscript and agree with them.
  - 2. Per journal style, you may list a maximum of 2 degrees here. Please remove one of your degrees here in the byline and below in your Corresponding Author information. Thank you for making this correction.
  - 3. If your paper is accepted for the Green Journal, we'll schedule it for our June issue until you let us know whether it's accepted for the 2020 ACOG ACSM. We are cautiously waiting to hear from ACOG. We will notify you as soon as we informed of the decision.
  - 4. Line 59: This should read "There was no difference identified in the rate of readmission for VTE between exposed and unexposed women. Of these, 7....... We have made this correction (now lines 60 to 61) and also in the Results section, line 158.
  - 5. Line 65: I'm uncertain what sentence on Line 66 means. What does 'more women....were younger" mean? Younger than what? Or do you mean, "Women that underwent contraceptive implant placement were younger and were more likely to have government-sponsored health insurance, to have smoked, and to have had hypertension than...."

We have clarified lines 66 to 70. Thank you for the suggestion.

6. Line 69: This sentence should read something like "After adjusting for these confounders, there remained no difference in rates of VTE....."

Thank you, we have made this suggested edit.

7. Line 71: Your results show no difference and are underpowered to do so. Therefore, you cannot conclude that the rate in exposed is "low" compared to women without the placement You can conclude that you did not show an increased risk of VTE in exposed women, but were underpowered to show a protective effect.

We have gone through the manuscript carefully and indicated while the immediate postpartum placement of the etonogestrel contraceptive implant was not associated with an increase rate of VTE, our sample size was underpowered to determine no difference.

8. Line 92: Sorry to just be catching this on this edit: This is known as a primacy claim: yours is the first, biggest, best study of its kind. In order to make such a claim, please provide the databases you have searched (PubMed, Google Scholar, EMBASE for example), the dates of your search, and the search terms used. If not done, please edit it out of the paper.

Thank you for pointing this out to us. We have deleted the line.

9. Line 153: Edit from, "Of women readmitted....", as recommended in the abstract comments.

We have made this edit as suggested on line 158.

10. Line 164: As with the comments in the abstract section, please edit the discussion section to reflect the inability to note a difference in the two groups. It's terrific that there is not an increase—you just cannot show a protective effect.

We have gone through the manuscript making sure to reflect that our sample size limited the determination of an association between exposure and the health outcome.

11. Line 172: Again, you need to talk about underpowered characteristic for detecting a protective effect.

We have edited the Discussion to reflect this point on lines 170, 179, and 234.

12. Line 195: It would be balanced to add that there is some concern that women receiving Medicaid insurance are disproportionately encouraged to use LARC due to systematic bias.

We have added a statement on lines 204 to 206.