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: Sep 23, 2019
To: "Matthew E Spotnitz" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-19-1530

RE: Manuscript Number ONG-19-1530

Relative risk of cervical neoplasms among copper and levonorgestrel intrauterine device users

Dear Dr. Spotnitz:

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

If you wish to consider revising your manuscript, you will first need to study carefully the enclosed reports submitted by the referees and editors. Each point raised requires a response, by either revising your manuscript or making a clear and convincing argument as to why no revision is needed. To facilitate our review, we prefer that the cover letter include the comments made by the reviewers and the editor followed by your response. The revised manuscript should indicate the position of all changes made. We suggest that you use the "track changes" feature in your word processing software to do so (rather than strikethrough or underline formatting).

Your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Oct 14, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

REVIEWER #1:

Review of Manuscript ONG-19-1530 "Relative risk of cervical neoplasms among copper and levonorgestrel intrauterine device users"

Spotnitz and colleagues have present data from Columbia University that is contained within the OHDSI network. The authors report using propensity scoring to help strengthen their findings. As noted below, there seem to be several examples of the reported data not being consistent in the manuscript/abstract. I have the following questions and comments for the authors.

Title - Should note it is a retrospective review/analysis

Précis - Acceptable

Abstract - Can you explain the discrepancy in the propensity group in the abstract 7114 CU-IUD and 2174 LNG-IUS vs. 7118 and 2175 from line 261 in the results? In addition the numbers noted for cases/person-years in the abstract were Cu- 2.42 cases/1000 person years vs. LNG - 5.16 cases/1000 person years although in the results they are Cu 2.36/1000 person years and LNG 4.89/1000 person years (lines 272-3).

Introduction - How do you know that progestational IUDs were under-represented if they were available from 1976-2001? Is there data from the cited review (I appreciate type was not collected/reported) such as year of the study that would support this assertion? If so please site - you do allude to this later in discussion but again this supporting claim, if data exists, such be referenced.

Methods - Why the limitation to 365 days prior (line 172)? Line 174 - prior IUD insertion - how were patients handled that had multiple LNG-IUS placed - excluded since they had a prior IUD placed? Using the IUD insertion date of any time after 1/1/2003 does that mean that the earlies time for the 365 prior observation was thus 1/1/2002? What do you mean by ITT for this study - since patients were not randomized to one therapy or another I am unclear how this would be utilized? Are you inferring that if there was a note to place a LNG-IUS and at the placement say one was not available and the patient received a Cu-IUD that they would be counted as "receiving an LNG-IUS" instead of the Cu-IUD they actually received? What if there was prolonged period of time where this happened for months because of supply issues?

Results -Was the mean age statistical different between the 2 groups? Why were other traditional risk factors like smoking not collected - I would suspect you would have data on at least 50% of the individuals even if it is binary - smoking ever

vs. never - consistent with only have race data on 50%. In Line 251-3 you not that women with Cu-IUD were less likely to have cervical cancer screening and/or preventative health visits than those with LNG-IUD. Is this a potentially fatal flaw in that if you don't perform screening you cannot find the outcome in question? Line 292 - how might the discrepancies for the validation cohort presented impact the outcomes?

Discussion - Address many of the potential strengths and limitations although at times seem to downplay potential concerns about limitations such as absent screening data, etc. In addition, common risk factors for dysplasia (smoking, age at first intercourse, etc. are missing). Perhaps since the high mean age for the Cu-IUD patients is a surrogate for a more mature and perhaps lower risk population than the younger LNG-IUD patients?

Tables - Why is table 1 referred to so far down in the results? Also did you consider placing more standard demographics in table 1 - how about smoking for instance which has a clear association with cervical dysplasia?

Figures - As depicted the scale for the survival probability on the Y axis could be considered misleading as it accentuates the changes present as the scale starts at 96%.

REVIEWER #2:

Thank you for this important review. Please respond to the following:

Introduction
Lines 142-43 Do you have a reference for the suggestion that copper ions increase the clearance rate of HPV?

Methods
Lines 178-79 Would specify SNOMED codes utilized. Were SNOMED terms used for specific diagnoses of CIN II (285838002) and CIN III (92564006)? Was CIN III severe dysplasia (20365006) also included?
Lines 206-7 Did the propensity score model include tobacco use? Given the known association between smoking and cervical cancer, this should be mentioned. Why isn't smoking included in Table 1?

Results
Lines 253-259 are confusing. If the outcome is defined as CIN II or III, why is there a different result reported for outcome lines 254 and 258 versus results reported specifically for CIN II and III?

REVIEWER #3:

In this manuscript, the authors compared the risk of developing high grade cervical intraepithelial neoplasia (CIN) and cancer among copper and levonorgestrel IUD users. The authors' conclusion that LNG-IUS users have a higher risk of high-grade CIN/cervical cancer compared to Cu-IUD users may not entirely be supported by their results because of potentially confounding variables that are not detailed in the manuscript.

Introduction

1. The authors cite a systematic review of 17 studies that describe a protective effect against cervical cancer among IUD users compared to non-users. Yet, the authors do not include a group of non-IUD users in this analysis and do not describe why they have chosen not to include this "non-user" group. This paper would be improved if such a control group was included to place the risk of IUD use in context.

2. The biologic mechanisms of Cu-IUD and LNG-IUS that may lead to differential risk of CIN/cervical cancer are not substantially supported and borderline on speculative leaving me to still wonder why the authors thought this was such an important topic to study.

Methods

1. One potential confounder that was not mentioned in the study was previous diagnosis of high-risk HPV infection. Was this one of the covariates evaluated in the model? Given that it can take several years from high-risk HPV acquisition to development of CIN/cervical cancer, why was the observation period begun 365 days prior to IUD insertion and not some longer duration such a 2-5 years?

2. Line 199. Why wasn't IUD removal included as an event that would end the observation period? Do the authors believe that the protective/harmful effects of the device would persist after removal? If so, what evidence supports this belief?

3. Lines 206-207. My main difficulty with this manuscript is the lack of clarity about covariates included in the model. Which ones were included? Which covariates were most associated with the outcome? Some that come to mind include age, parity, medical co-morbidities, differences in cervical cancer screening rates, smoking status, previous HPV infection

or abnormal pap smear, number of sexual partners which may be different among Cu-IUD and LNG-IUS users and may have contributed to differential CIN/cervical cancer risk. Since many of these are not outlined in the study, it is hard to make any conclusion about the validity of results. Was there a conceptual model used to inform the model design?

4. Along those lines, which were some of the strongest negative control diagnoses?

5. Did the authors perform any a priori sample size calculations to detect a significant difference in such a rare outcome? If not, why not? If so, please include.

Results

1. There were many more Cu-IUD compared to LNG-IUS users in this study. Does this match the national trend? If not, why do the authors believe there were so many more Cu-IUD users in this cohort and how would this influence the generalizability of results?

2. The median follow-up observation period was 10 person-years, yet it can take 15+ years for CIN/cervical cancer to develop. This is a potential limitation of the study.

3. Lines 244-245. Given the large amount of missing race/ethnicity data, how reliable is this dataset regarding the other covariates included? Along those lines, the amount of missing data should be included in Table 1.

4. Line 248. Was prior HPV vaccination assessed for the year prior to IUD insertion or over the lifetime? Given the mean age of 37 and 33 years for respective IUD placement, this variable may be misclassified and unreliable if only evaluated for a year prior.

5. Lines 251 to 253. A significant difference between the Cu-IUD and LNG-IUS is duration of use of 10 years versus 5 years. This may make Cu-IUD users less likely to return for cervical cancer screening (as found in your study) and thus less likely to receive a diagnosis of CIN/cervical cancer within the observation period. How was this addressed in your study to clarify that it was the device type, and not differences in screening rates, that was associated with the outcome?

6. Lines 255-259. What was the time to development of CIN/cervical cancer from device placement for each method?

7. Lines 286-288. Should the results of the Kaplan-Meier plot be interpreted to indicate that longer duration of the LNG-IUS use is associated with a greater risk of CIN/cervical cancer? Does this account for device removal? What about additional risk factors for high-risk HPV acquisition which may decrease over time such a new sexual partners, concurrent sexual partners? Figure 1 seems to indicate a large area of overlap in the confidence interval beyond 2000 days. How should the reader interpret that?

8. Lines 293-295. Approximately 900 participants could be misclassified as using Cu-IUD when in fact they received LNG-IUS. Does this change the results?

Discussion

1. The authors conclude essentially saying that if one uses an LNG-IUS they are at greater risk for cervical cancer than Cu-IUD users. This is a very strong statement and may not be supported by these research methods. As I mentioned above, putting this risk in context with non-users is very important. Clarification of the potential confounders evaluated beyond age, race/ethnicity, HPV vaccination, and estrogen exposure is also very important to put this risk into context.

2. Lines 305-306. I don't understand this sentence.

3. Lines 347-348. The authors state they have no reason to believe that cervical neoplasms would have been differentially missed, but how can that be explained in light of the lower cervical cancer screening rate in the Cu-IUD group?

4. Lines 363-364. Which covariates related to socioeconomic status were included?

STATISTICAL EDITOR'S COMMENTS:

1. Table 1: Some of the %s are incorrect (eg. 895/2039=43.9%, not 41%). Since all denominators were > 1000, should cite %s to nearest 0.1%. Also, our readers would likely be more accustomed to a comparing the proportions pre and post PS matching as a column of p-values, so should use that format. If the Authors desire, could provide the std diff in a separate on-line table.

2. Tables 2 and 3: Should include 95% CIs for the incidence rates. Given the number of events, should round the estimates and CIs to 0.1 cases/!K persons or 0.1 cases per 1K person-years precision. Rather than "days at risk", should change to person-years.

3. Fig 1: Survival analysis was the method used, but the y-axis does not show survival, but rather, proportion without neoplasm. I presume some test of difference (ie, log-rank was done). Should indicate in legend or figure the test and significance.

4. lines 146-231: Although much of this description of methods is important, it is likely not of interest to our clinician readers. Should include most of the technical details, along with explanations of appendices to on-line material, with a concise summary in main text.

5. lines 244-248: This is a potentially important limitation, since race/ethnicity could be an important confounder.

6. lines 248: Were there any data re: prior HPV infections among these women. If so, should do sensitivity analysis by separate analysis. If no information was present in the database, then that could also be an important unaccounted confounder.

7. General: cases per 1000 years is cited multiple times in the text. Should be "cases per 1000 person-years"

8. lines 286-288: I suspect that there is insufficient data to allow sufficient stats power to compare the slopes at various time points, but if the Authors want to perform that formal analysis, then should include. Otherwise, the observation of changing slope has no statistical basis and should be omitted from discussion. Suffice to say that the two curves were/were not statistically divergent.

9. lines 292-295: Should validate a larger random sample to verify that women generally (with or without neoplasms) were allocated correctly into Cu-IUD vs LNG-IUS categories, since mis allocation would affect the incidence rates.

10. lines 295-296: What were the results of analysis if limited to "retrievable biopsy confirmation"?

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. In order for an administrative database study to be considered for publication in Obstetrics & Gynecology, the database used must be shown to be reliable and validated. In your response, please tell us who entered the data and how the accuracy of the database was validated. This same information should be included in the Materials and Methods section of the manuscript.

4. Responsible reporting of research studies, which includes a complete, transparent, accurate and timely account of what was done and what was found during a research study, is an integral part of good research and publication practice and not an optional extra. Obstetrics & Gynecology supports initiatives aimed at improving the reporting of health research, and we ask authors to follow specific guidelines for reporting randomized controlled trials (ie, CONSORT), observational studies (ie, STROBE), meta-analyses and systematic reviews of randomized controlled trials (ie, PRISMA), harms in systematic reviews (ie, PRISMA for harms), studies of diagnostic accuracy (ie, STARD), meta-analyses and systematic reviews of observational studies (ie, MOOSE), economic evaluations of health interventions (ie, CHEERS), quality improvement in health care studies (ie, SQUIRE 2.0), and studies reporting results of Internet e-surveys (CHERRIES). Include the appropriate checklist for your manuscript type upon submission. Please write or insert the page numbers where each item appears in the margin of the checklist. Further information and links to the checklists are available at http://ong.editorialmanager.com. In your cover letter, be sure to indicate that you have followed the CONSORT, MOOSE, PRISMA, PRISMA for harms, STARD, STROBE, CHEERS, SQUIRE 2.0, or CHERRIES guidelines, as appropriate.

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, references, 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. 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.

10. 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.

11. 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%").

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. The Journal's Production Editor had the following to say about the figures in your manuscript:

"Figure 1: Please upload as a figure file on Editorial Manager."

When you submit your revision, art saved in a digital format should accompany it. If your figure was created in Microsoft Word, Microsoft Excel, or Microsoft PowerPoint formats, please submit your original source file. Image files should not be copied and pasted into Microsoft Word or Microsoft PowerPoint.

When you submit your revision, art saved in a digital format should accompany it. Please upload each figure as a separate file to Editorial Manager (do not embed the figure in your manuscript file).

If the figures were created using a statistical program (eg, STATA, SPSS, SAS), please submit PDF or EPS files generated directly from the statistical program.

Figures should be saved as high-resolution TIFF files. The minimum requirements for resolution are 300 dpi for color or black and white photographs, and 600 dpi for images containing a photograph with text labeling or thin lines.

Art that is low resolution, digitized, adapted from slides, or downloaded from the Internet may not reproduce.

14. 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.

***

If you choose to revise your manuscript, please submit your revision through Editorial Manager at http://ong.editorialmanager.com. Your manuscript should be uploaded in a word processing format such as Microsoft Word. Your revision's cover letter should include the following:

* A confirmation that you have read the Instructions for Authors (http://edmgr.ovid.com/ong/accounts/authors.pdf), and
* A point-by-point response to each of the received comments in this letter.

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

Again, your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Oct 14, 2019, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

The Editors of Obstetrics & Gynecology

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

_____

Relative risk of cervical neoplasms among copper and levonorgestrel intrauterine device users

Dear Dr. Spotnitz:

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

If you wish to consider revising your manuscript, you will first need to study carefully the enclosed reports submitted by the referees and editors. Each point raised requires a response, by either revising your manuscript or making a clear and convincing argument as to why no revision is needed. To facilitate our review, we prefer that the cover letter include the comments made by the reviewers and the editor followed by your response. The revised manuscript should indicate the position of all changes made. We suggest that you use the "track changes" feature in your word processing software to do so (rather than strikethrough or underline formatting).

Your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Oct 14, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

REVIEWER #1:

Review of Manuscript ONG-19-1530 "Relative risk of cervical neoplasms among copper and levonorgestrel intrauterine device users"

Spotnitz and colleagues have present data from Columbia University that is contained within the OHDSI network. The authors report using propensity scoring to help strengthen their findings. As noted below, there seem to be several examples of the reported data not being consistent in the manuscript/abstract. I have the following questions and comments for the authors.

Title - Should note it is a retrospective review/analysis

Précis - Acceptable

Abstract - Can you explain the discrepancy in the propensity group in the abstract 7114 CU-IUD and 2174 LNG-IUS vs. 7118 and 2175 from line 261 in the results?

After propensity score adjustment, there were 7118 patients in the Cu-IUD cohort and 2175 patients in the LNG-IUS cohort. An algorithm filtered 4 Cu-IUD users and 1 LNG-IUS user from the analysis because of insufficient data (lines 295-296). No changes to the text.

In addition the numbers noted for cases/person-years in the abstract were Cu- 2.42 cases/1000 person years vs. LNG - 5.16 cases/1000 person years although in the results they are Cu 2.36/1000 person years and LNG 4.89/1000 person years (lines 272-3).

Both sets of numbers are accurate. The former group of numbers was derived from propensity score stratification (lines 300-308) and the latter was from propensity score matching (lines 310-319). We reported the propensity score matching results in the abstract (lines 116-121) because of less residual confounding. The reproducibility between the different statistical methods is reassuring that our results were accurate. The reason we present both results is to reassure the reader. We will happily report in the abstract whichever numbers the editor or reviewer feel are more presentable and have rounded the rates to a single decimal.

Introduction - How do you know that progestational IUDs were under-represented if they were available from 1976-2001? Is there data from the cited review (I appreciate type was not collected/reported) such as year of the study that would support this assertion? If so please site - you do allude to this later in discussion but again this supporting claim, if data exists, such be referenced.

According to the FDA application for the Mirena (reference#14, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/21-225.pdf_Mirena_Medr.pdf), the Mirena was not approved in the United States until 2000 and the phase III contraception trials that evaluated the device occurred between 1982 to 1996. Additionally, the LNG-IUS was first approved in Finland, Italy, and Spain in the years 1990, 1996 and 2000, respectively. For the 16 case-control studies that were harmonized by Cortessis et. al. (reference #1, Cortessis VK, Barret M, Wade NQ et. al. *Intrauterine device use and cervical cancer risk: A systematic review and meta-analysis*. Obstetrics & Gynecology (2017) 130(6): 1226-1236), none of the sites had an LNG-IUS that was approved for use during the study period. Thank you for this interesting point about global uptake of LNG-IUS. Lines 153-157 have been updated accordingly.

Methods - Why the limitation to 365 days prior (line 172)?

We wanted to have patients in our database for at least 365 days so we could have adequate data for propensity score adjustment. Additionally, patients who were observed in our database for at least 365 days prior to IUD placement were more likely to report for follow up screening. No change to the text.

Line 174 - prior IUD insertion - how were patients handled that had multiple LNG-IUS placed - excluded since they had a prior IUD placed?

A woman who had multiple IUDs or IUSs placed entered the cohort at the time of the first device placement and continued thereafter. A woman who had both an Cu-IUD and an LNG-IUS placed was considered part of the LNG-IUS cohort starting at the time of first device placement. For example, a woman who had an LNG-IUS placed and then a Cu-IUD was assigned to the LNG-IUS cohort. A woman who had a Cu-IUD placed and then an LNG-IUS was also assigned to the LNG-IUS group, starting at the time of Cu-IUD placement. Since the LNG-IUS cohort had a greater proportion of cervical neoplasms, correcting for this unidirectional misclassification error would have shifted our results away from the null.

Using the IUD insertion date of any time after 1/1/2003 does that mean that the earlies time for the 365 prior observation was thus 1/1/2002?

The patients needed to have at least 365 days of prior medical observation and to have been observed at least once in the most recent 365 days. At a minimum, a patient could begin observation in our database on 1/1/2002, but many were likely to have been observed for a longer period of time. No change to the text.

What do you mean by ITT for this study - since patients were not randomized to one therapy or another I am unclear how this would be utilized?

Patients were assigned to a group based on initial exposure to either Cu-IUD or LNG-IUS. This study design is similar to an any-use analysis, which was used in the case-control studies described in reference #1(Cortessis VK, Barret M, Wade NQ et. al. *Intrauterine device use and cervical cancer risk: A systematic review and meta-analysis*. Obstetrics & Gynecology (2017) 130(6): 1226-1236),) and is cited on line 152. One advantage on ITT or any use design is that it avoids selection bias from incomplete data on device removal. We are aware that this terminology is misleading and are using the term "any-use" instead (line 217).

Are you inferring that if there was a note to place a LNG-IUS and at the placement say one was not available and the patient received a Cu-IUD that they would be counted as "receiving an LNG-IUS" instead of the Cu-IUD they actually received? What if there was prolonged period of time where this happened for months because of supply issues?

Thank you for this interesting question. The index date of the IUD placement was when patients were billed for the CPT code associated with the procedure. No change to the text.

Results -Was the mean age statistical different between the 2 groups?

Thank you for addressing the mean age. The initial set of numbers reported for that variable were typographical errors and indicated the age of the women at follow up. Our corrected numbers show that the median age for both cohorts was 29 years.

Why were other traditional risk factors like smoking not collected - I would suspect you would have data on at least 50% of the individuals even if it is binary - smoking ever vs. never - consistent with only have race data on 50%.

Thank you for this interesting point. We have binary data on smoking history, which we matched upon and included in our propensity score model. Additionally, we expect to have adjusted for the effects of smoking indirectly by balancing on other covariates that are associated with smoking history.

By crude characterization, the number of women who had a claim or diagnosis of smoking prior to device placement was 3629 (43.9%) in the Cu-IUD cohort and 1401 (58.4%) in the LNG-IUS cohort. Within 1 year prior to IUD placement, we identified 3261 women in the Cu-IUD cohort and 1290 in the LNG-IUS cohort, and adjusted for them in our propensity score model. After adjustment by

propensity score matching, the magnitude of the standard deviation of the mean of this covariate was less than 0.02 between the cohorts.

In the largest observational cohort study about the relative contraceptive failure rates of Cu-IUDs and LNG-IUSs, which consisted of more than 50,000 patients, Heinemann et. al. found that the proportion of smokers in the Cu-IUD and LNG-IUS cohorts was comparable (K. Heinemann et. al. *Risk of uterine perforation with levonorgestrel-releasing and copper intrauterine devices in the European Active Surveillance Study on Intrauterine Devices* Contraception 91(4) (2015) 274-279). We expect that the magnitude of confounding by smoking history was minimal in our crude analysis and less after propensity score adjustment. We appreciate the insightful comment and have updated Table 1 with data about smoking history within 1 year prior to IUD placement (lines 510-511).

In Line 251-3 you not that women with Cu-IUD were less likely to have cervical cancer screening and/or preventative health visits than those with LNG-IUD. Is this a potentially fatal flaw in that if you don't perform screening you cannot find the outcome in question? Line 292 - how might the discrepancies for the validation cohort presented impact the outcomes?

We agree that women who are not screened will not get the outcome. Therefore, we balanced the differential uptake of screening at baseline with propensity score adjustment. Any imbalance between screening uptake during the study interval could arguably be an effect of the device placement and adjusting for it would be conditioning upon an intermediate. Therefore, we did not adjust on screening uptake after the index date to avoid bias.

By crude analysis, the proportions of women who had at least one cervical cancer screening procedure after the index event in the Cu-IUD and LNG-IUS were similar (30.9% vs. 34.8%, respectively). Therefore, we do not expect large differences in uptake of screening during the study interval. Additionally, the number of tests a patient receives during the study interval is dependent on whether the tests are abnormal, and conditioning upon that covariate could lead to biased results. Therefore, we did not adjust for the number of screening tests during the study interval. No change to the text.

Discussion - Address many of the potential strengths and limitations although at times seem to downplay potential concerns about limitations such as absent screening data, etc. In addition, common risk factors for dysplasia (smoking, age at first intercourse, etc. are missing). Perhaps since the high mean age for the Cu-IUD patients is a surrogate for a more mature and perhaps lower risk population than the younger LNG-IUD patients?

We acknowledge having data on all of these variables would be ideal for analysis, however their effects can be adjusted indirectly with propensity score stratification and matching on other covariates. We have added a few sentences (lines 368-371) that explain how these variables could have confounded the analysis and therefore propensity score adjustment was necessary. As noted above, the reported difference in age was a typographical error. The corrected median ages are the same. Thank you for this insightful point. No change to the text.

Tables - Why is table 1 referred to so far down in the results? Also did you consider placing more standard demographics in table 1 - how about smoking for instance which has a clear association with cervical dysplasia?

Thank you for this insightful point. We have changed the text to mention table 1 at the start of the second paragraph in the results (line 266). As noted above, we have added smoking history within 1 year of device placement to table 1.

Figures - As depicted the scale for the survival probability on the Y axis could be considered misleading as it accentuates the changes present as the scale starts at 96%.

We believe that we have followed the usual conventions for plotting Kaplan-Meier plots, and have shown both curves on the same axis. We would be happy to make whatever changes the reviewers consider appropriate.

REVIEWER #2:

Thank you for this important review. Please respond to the following:

Introduction
Lines 142-43 Do you have a reference for the suggestion that copper ions increase the clearance rate of HPV?

Yes, Lekovich et. al. stated in reference#2 that copper ions increase the clearance rate of HPV (Lekovich JP, Amrane S, Pangasa M et. al. *Comparison of human papillomavirus infection and cervical cytology in women using copper-containing and levonorgestrel-containing intrauterine Devices.* Obstetrics & Gynecology (2015) 125(5):1101-5.).

Methods
Lines 178-79 Would specify SNOMED codes utilized. Were SNOMED terms used for specific diagnoses of CIN II (285838002) and CIN III (92564006)? Was CIN III severe dysplasia (20365006) also included?

Yes, we differentiated CIN II and CIN III by SNOMED codes. CIN III with severe dysplasia (20365006) was included among our list of condition codes for high grade cervical neoplasms.

Lines 206-7 Did the propensity score model include tobacco use? Given the known association between smoking and cervical cancer, this should be mentioned. Why isn't smoking included in Table 1?

As noted in our response to reviewer#1, we have binary data on smoking history that we matched upon and included in our propensity score model. Additionally, we expect to have adjusted for the effects of smoking indirectly by balancing on other covariates that are associated with smoking history.

By crude characterization, the number of women who had a prior smoking observation at baseline were 3629 (43.9%) in the Cu-IUD cohort and 1401 (58.4%) in the LNG-IUS cohort. Within 1 year prior to IUD placement, we identified 3261 women in the Cu-IUD cohort and 1290 in the LNG-IUS cohort, and adjusted for them in our propensity score model. After adjustment by propensity score

matching, the magnitude of the standard deviation of the mean of this covariate was less than 0.02 between the cohorts.

In the largest observational cohort study about the relative contraceptive failure rates of Cu-IUDs and LNG-IUSs, which consisted of more than 50,000 patients, Heinemann et. al. found that the proportion of smokers in the Cu-IUD and LNG-IUS cohorts was comparable (K. Heinemann et. al. *Risk of uterine perforation with levonorgestrel-releasing and copper intrauterine devices in the European Active Surveillance Study on Intrauterine Devices* Contraception 91(4) (2015) 274-279). We expect that the magnitude of confounding by smoking history was minimal in our crude analysis and less after propensity score adjustment. We appreciate the insightful comment and have updated Table 1 with data about smoking history within 1 year prior to IUD placement (lines 510-511).

In looking at the morphology and quantity of propensity score distribution overlap, the cohorts appear almost naturally comparable on inspection. We have decided to move the first figure from the appendix at make it the new figure 1 to highlight the excellent overlap of the cohorts at baseline. However, we only studied the patients that were balanced after propensity score matching or stratification (lines 368-369). We are attaching a representative number of variables from the propensity score model into this response letter.

Results
Lines 253-259 are confusing. If the outcome is defined as CIN II or III, why is there a different result reported for outcome lines 254 and 258 versus results reported specifically for CIN II and III?

Thank you for highlighting this source of confusion. Our set of outcomes codes included more than CIN II or III. We looked at the proportion of patients who were diagnosed with any cervical neoplasia code as well as the subgroup of patients who were diagnosed with CIN II or III. We have clarified this point in the text (lines 283-5).

REVIEWER #3:

In this manuscript, the authors compared the risk of developing high grade cervical intraepithelial neoplasia (CIN) and cancer among copper and levonorgestrel IUD users. The authors' conclusion that LNG-IUS users have a higher risk of high-grade CIN/cervical cancer compared to Cu-IUD users may not entirely be supported by their results because of potentially confounding variables that are not detailed in the manuscript.

Introduction

1. The authors cite a systematic review of 17 studies that describe a protective effect against cervical cancer among IUD users compared to non-users. Yet, the authors do not include a group of non-IUD users in this analysis and do not describe why they have chosen not to include this "non-user" group. This paper would be improved if such a control group was included to place the risk of IUD use in context.

We agree that a direct comparison with non-users would be an interesting and relevant analysis. However, we designed a comparative effectiveness study that measured the relative risk of high grade neoplasms of Cu-IUD to LNG-IUS users. Second, it would be difficult to define a cohort of non-users that is similar to a cohort of IUD users. IUD users intend to use the same method of contraception continuously for years. Oral contraceptive pill users, by contrast, are more likely to discontinue contraception, give birth or change the contraception method during the study period. Additionally, oral contraceptive use in itself is very common and a risk factor for cervical neoplasms, for which we may not be able to adjust. We have made the lack of comparison between LNG-IUS users and women who do not use IUDs a point of the discussion (line 364-366) and the final point of our manuscript (line 405-407).

2. The biologic mechanisms of Cu-IUD and LNG-IUS that may lead to differential risk of CIN/cervical cancer are not substantially supported and borderline on speculative leaving me to still wonder why the authors thought this was such an important topic to study.

In the FDA application for the Mirena (reference#14, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/21-225.pdf_Mirena_Medr.pdf, Medical Review, Section 6.3), which reported data from a randomized control trial that compared a LNG-IUS to a Cu-IUD, the incidence of high grade cervical neoplasms for the LNG-IUS cohort was 1.8% and 1.4% in the Cu-IUD cohort. That RCT was underpowered to evaluate the rare outcome of high grade cervical neoplasia. Consistently, we have found that the incidence of high grade cervical neoplasms among the LNG-IUS cohort was 0.5% greater than the Cu-IUD cohort and our population is large enough for these results to be statistically significant. The fact that our observational data are showing an effect that is consistent with what was previously reported in an RCT is reassuring that the confounding is minimal and the effect is real. These points were addressed in lines 338-340. No change to the text.

We hope that our study generates interest in understanding the biochemical mechanism behind these findings, which we agree are not well known. Our study has implications both for the relative safety of different types of intrauterine contraceptive devices, which are used in 100 million women worldwide, and may provide unique insights into the pathophysiology of cervical neoplasms. The public health impact of this study is discussed in lines 398-402. No change to the text.

Methods

1. One potential confounder that was not mentioned in the study was previous diagnosis of high-risk HPV infection. Was this one of the covariates evaluated in the model? Given that it can take several years from high-risk HPV acquisition to development of CIN/cervical cancer, why was the observation period begun 365 days prior to IUD insertion and not some longer duration such a 2-5 years?

The observation period started with the date of IUD placement. Patients were in the hospital database for a minimum of 365 days, and could have been in the system for a longer period of time. By crude characterization, the incidences of women who had a positive lab test for HPV at baseline were 542 (6.5%) in the Cu-IUD cohort and 181 (7.5%) in the LNG-IUS cohort. Within 1 year of IUD placement, we identified 210 women in the Cu-IUD cohort and 59 women in the LNG-IUS cohort who had a positive HPV lab test. After adjustment with propensity score matching, the magnitude

standard deviation of the mean between these groups was less than 0.06. Therefore, we used propensity score matching to reduce baseline confounding by high risk HPV infection.

We agree that HPV is important. Since the start date of our study period was 2003, when HPV was not routinely done, we did not have data on high risk infection for all patients during the study period. We adjusted for HPV infection to the extent that it was possible.

2. Line 199. Why wasn't IUD removal included as an event that would end the observation period? Do the authors believe that the protective/harmful effects of the device would persist after removal? If so, what evidence supports this belief?

Patients were assigned to a group based on initial exposure to either Cu-IUD or LNG-IUS, as an any-use analysis. Our study design is similar to a meta-analysis of 17 any-use case-control reports that was published in this journal recently by Cortessis et. al. (reference#1, Cortessis VK, Barret M, Wade NQ et. al. *Intrauterine device use and cervical cancer risk: A systematic review and meta-analysis.* Obstetrics & Gynecology (2017) 130(6): 1226-1236).

One advantage on ITT or any use-design is that it avoids selection bias from incomplete data on device removal. Thank you for this interesting point. We have changed the text to accordingly (line 217).

3. Lines 206-207. My main difficulty with this manuscript is the lack of clarity about covariates included in the model. Which ones were included? Which covariates were most associated with the outcome? Some that come to mind include age, parity, medical co-morbidities, differences in cervical cancer screening rates, smoking status, previous HPV infection or abnormal pap smear, number of sexual partners which may be different among Cu-IUD and LNG-IUS users and may have contributed to differential CIN/cervical cancer risk. Since many of these are not outlined in the study, it is hard to make any conclusion about the validity of results. Was there a conceptual model used to inform the model design?

We agree that the covariate model is very important to this kind of analysis. As supplementary information, we are including a representative group of variables that were used in the model. Thank you for this interesting point.

4. Along those lines, which were some of the strongest negative control diagnoses?

Thank you for your interest in our negative controls. The ones that had the lowest p values were "Benign neoplasm of skin of trunk", "Sprain of ankle" and "senile hyperkeratosis." Overall, calibration with negative controls did not change our analysis and we report uncalibrated results as our main finding. No change to the text.

5. Did the authors perform any a priori sample size calculations to detect a significant difference in such a rare outcome? If not, why not? If so, please include.

No a priori sample size calculation was performed, because we used all available data instead of a sample. The fact that we reported an effect with a p-value less than 0.05, indicates that the study population size was adequate. No change to the text.

Results

1. There were many more Cu-IUD compared to LNG-IUS users in this study. Does this match the national trend? If not, why do the authors believe there were so many more Cu-IUD users in this cohort and how would this influence the generalizability of results?

Yes, this matches a national and global trend. Cu-IUDs came onto the market may years before the LNG-IUSs, are less expensive and more prevalent worldwide. and are more prevalent worldwide. Thank you for this interesting question about use of intrauterine contraception. No change to the text.

2. The median follow-up observation period was 10 person-years, yet it can take 15+ years for CIN/cervical cancer to develop. This is a potential limitation of the study.

We agree that this is a potential limitation of the study. A longer follow-up observation period would be helpful because of the lag between HPV infection and cervical neoplasms. However, our study period is the maximum amount of observation time for this analysis. The LNG-IUS was FDA approved in 2000, and began to be used in our medical center in 2003. Our study period is from 2003 through December 2018, which is the end of the observation period of our database. We intend to follow up this analysis with an OHDSI network study that will include other databases that may have more long term data. No change to the text.

3. Lines 244-245. Given the large amount of missing race/ethnicity data, how reliable is this dataset regarding the other covariates included? Along those lines, the amount of missing data should be included in Table 1.

All of the other covariates come from medical diagnoses and billing codes. The front desk staff are required to enter race and ethnicity data, are often uncertain in their entry, and not as required to provide high quality data.

4. Line 248. Was prior HPV vaccination assessed for the year prior to IUD insertion or over the lifetime? Given the mean age of 37 and 33 years for respective IUD placement, this variable may be misclassified and unreliable if only evaluated for a year prior.

This is a lifetime measurement of prior HPV vaccination that occurred between all days and 1 day prior to intrauterine device placement, and while the patient was in our database. Many of the women in the cohort did not have the opportunity for the vaccination.

As noted in response to reviewer #1, both cohorts actually had a median age of 29.
The HPV vaccine was first licensed in 2006, for women under the age of 26. Women in the first 3 years of the cohort never had any chance of the vaccine. After 2006, a lot of women were out of the age range to receive it. Therefore, many of the women in the cohort never would have been

offered the vaccine. We balanced the groups with regard to HPV exposure in our propensity score model.

We agree that we may have missed a vaccine that could have happened outside of this hospital, however we do not believe that the proportions of Cu-IUD and LNG-iUS users who received a vaccine at another hospital were markedly different. In our crude characterization, the proportions of patients who received an HPV vaccine in this hospital were similar and small for the Cu-IUD and LNG-IUS cohorts (0.5% vs. 1.6%, respectively), and we suspect that they were similar outside of this hospital as well.

5. Lines 251 to 253. A significant difference between the Cu-IUD and LNG-IUS is duration of use of 10 years versus 5 years. This may make Cu-IUD users less likely to return for cervical cancer screening (as found in your study) and thus less likely to receive a diagnosis of CIN/cervical cancer within the observation period. How was this addressed in your study to clarify that it was the device type, and not differences in screening rates, that was associated with the outcome?

As per prior response, we balanced on many covariates at baseline that are associated with uptake of screening and other preventive care. We excluded women who were unbalanced on these variables. As per prior response, the uptake of cervical screening between the cohorts was similar during the study period.

By inspection, the Kaplan-Meier curves started to diverge at approximately 6-12 months following IUD placement. Since this effect starts to become apparent before a 5 year period, the differences in duration of use or follow-up after 5 years are unlikely to affect the magnitude of our findings substantially. No change to the text.

6. Lines 255-259. What was the time to development of CIN/cervical cancer from device placement for each method?

The minimum time to a diagnosis of the outcome was 30 days following placement. A subgroup analysis started at 365 days following placement. The concordance between the results of our main and subgroup analysis is reassuring that our observed effect is real. No change to the text. By inspection, the Kaplan-Meier curves diverged prior to a 5 year follow up period.

7. Lines 286-288. Should the results of the Kaplan-Meier plot be interpreted to indicate that longer duration of the LNG-IUS use is associated with a greater risk of CIN/cervical cancer?
It is unclear to what extent the higher incidence of cervical neoplasms in the LNG-IUS group is due to longer exposure. We did not report data on device removal, and therefore did not make an interpretation about device use. No change to the text.

Does this account for device removal?
We did not account for device removal out of concern that incomplete data could lead to a selection bias. No change to the text.

What about additional risk factors for high-risk HPV acquisition which may decrease over time such a new sexual partners, concurrent sexual partners?

Thank you for this interesting question about risk factors for high-risk HPV acquisition during the study period. We don't have data on the sexual behavior of our patients, but we assume it is balanced. Because the latent period between HPV infection and neoplasm diagnosis is typically 10 years, high-risk HPV acquisition during the study period is unlikely to manifest as a high grade cervical neoplasm. The fact that the mean age for both cohorts is 29, may be an indicator that the patients had comparable risk factors for high-risk HPV acquisition. No change to the text.

Figure 1 seems to indicate a large area of overlap in the confidence interval beyond 2000 days. How should the reader interpret that?

Beyond 2000 days, the number of patients in each cohort was small, which made the variance in our estimates large. Therefore, the confidence intervals were very wide. Thank you for this interesting question about variance. No change to the text.

8. Lines 293-295. Approximately 900 participants could be misclassified as using Cu-IUD when in fact they received LNG-IUS. Does this change the results?

Thank you for this insightful comment. The misclassification was unique to the Cu-IUD cohort. Correcting for this would shift the effect away from the null, since the LNG-IUS group had a higher incidence of cervical neoplasms. This point is addressed in lines 392-396. No change to the text.

Discussion

1. The authors conclude essentially saying that if one uses an LNG-IUS they are at greater risk for cervical cancer than Cu-IUD users. This is a very strong statement and may not be supported by these research methods. As I mentioned above, putting this risk in context with non-users is very important. Clarification of the potential confounders evaluated beyond age, race/ethnicity, HPV vaccination, and estrogen exposure is also very important to put this risk into context.

Our methodology is consistent with the 16 studies that were harmonized into a systematic review by Cortessis et. al. and published in this journal (reference#1, Cortessis VK, Barret M, Wade NQ et. al. *Intrauterine device use and cervical cancer risk: A systematic review and meta-analysis.* Obstetrics & Gynecology (2017) 130(6): 1226-1236). We agree that using a database for historical analysis has its limitations, however our results were consistent with the phase III RCT that compared LNG-IUS to Cu-IUD use for premarket approval (reference#14, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/21-225_Mirena.cfm**).**

We performed a comparative effectiveness study that reported relative risks. We are aware that we have not made a direct comparison to non-users, which is why we mentioned that the relative risk of LNG-IUS users to the general population is unknown (lines 361-366).

As supplementary information, we are including the propensity score model to clarify what variables were used to select the patients. As per prior response, it is difficult to design a study with

a control group of patients who do not use intrauterine devices as contraception. Therefore, we report relative effects.

2. Lines 305-306. I don't understand this sentence.

This line communicates that the proportions of patients who had HPV vaccines, and other baseline characteristics, are consistent with what we would expect for the patients who were studied in our cohorts since 2003. The sentence is omitted from text.

3. Lines 347-348. The authors state they have no reason to believe that cervical neoplasms would have been differentially missed, but how can that be explained in light of the lower cervical cancer screening rate in the Cu-IUD group?

Although the cervical cancer screening rates were unequal at baseline, we expect that after propensity score adjustment the cervical cancer screening rates were similar. After adjustment, we think it is very unlikely that cervical neoplasms were differentially missed. As stated in prior response, the proportion of patients with at least 1 cervical screening after insertion was similar between the cohorts at baseline. No change to the text.

4. Lines 363-364. Which covariates related to socioeconomic status were included?

All patients had access to screening. Other than uptake of screening, which we have adjusted for prior to the IUD placement, we do not have many direct measurements of socioeconomic status. However, we have no reasons to believe that the LNG-IUS users would be of lower socioeconomic status that Cu-IUD users. No change to the text.

STATISTICAL EDITOR'S COMMENTS:

1. Table 1: Some of the %s are incorrect (eg. 895/2039=43.9%, not 41%). Since all denominators were > 1000, should cite %s to nearest 0.1%. Also, our readers would likely be more accustomed to a comparing the proportions pre and post PS matching as a column of p-values, so should use that format. If the Authors desire, could provide the std diff in a separate on-line table.

Thank you for bringing this to our attention. We have revised and resubmitted. We apologize for making those errors.

2. Tables 2 and 3: Should include 95% CIs for the incidence rates. Given the number of events, should round the estimates and CIs to 0.1 cases/!K persons or 0.1 cases per 1K person-years precision. Rather than "days at risk", should change to person-years.

Thank you for this suggestion. We have updated the text accordingly in the abstract(lines 112-121), results(lines 303-306, 316-317), and tables (lines 565-566, and 609-610).

3. Fig 1: Survival analysis was the method used, but the y-axis does not show survival, but rather, proportion without neoplasm. I presume some test of difference (ie, log-rank was done). Should indicate in legend or figure the test and significance.

Thank you for this suggestion. We did not perform a log-rank calculation and have clarified that we are observing effects on inspection.

4. lines 146-231: Although much of this description of methods is important, it is likely not of interest to our clinician readers. Should include most of the technical details, along with explanations of appendices to on-line material, with a concise summary in main text.
We are happy to defer to the editor for additional changes of the description of statistical analysis.

5. lines 244-248: This is a potentially important limitation, since race/ethnicity could be an important confounder.

As per our answer to reviewer#3, front desk staff are required to enter race and ethnicity data, and are often uncertain in their entry. The data are not related to billing codes and often neglected.

We agree that race/ethnicity could be an important confounder and that it was unbalanced at baseline. By our crude analysis, the proportions of patients who were Black or African-American, White, and Hispanic or Latino in the Cu-IUD cohort were 6.2%, 25.3% and 32.0% compared to 8.7%, 31.7% and 32.0% in the LNG-IUS cohort. Therefore, we adjusted for those variables in our propensity score analysis. We have updated the discussion to include this limitation (line 379).

The rate of missing data was high for both cohorts and greater for the Cu-IUD cohort compared to the LNG-IUS cohort (64.5% and 54.7%, respectively). This is a common problem with this kind of analysis. We adjusted for measurable differences in race between the cohorts. However, we recognize that unmeasured covariates related to race could be a source of confounding in the study.

We know from SEER data that cervical cancer is more common among women of lower socioeconomic status. Cervical cancer is more common among non-white hispanics than blacks and more common among blacks than whites. Our data does not indicate to what extent socioeconomic status or racial identity determines the selection of intrauterine device contraception. However since the LNG-IUS is more expensive ,we find it unlikely that patients low socioeconomic status will be more likely to receive that device. However, we recognize that this is speculation, which is why we did not mention it in the manuscript directly.

6. lines 248: Were there any data re: prior HPV infections among these women. If so, should do sensitivity analysis by separate analysis. If no information was present in the database, then that could also be an important unaccounted confounder.

By crude characterization, the incidences of women who had a positive lab test for HPV at baseline were 543 (5.7%) in the Cu-IUD cohort and 181 (7.5%) in the LNG-IUS cohort. Within 1 year of IUD placement, we identified 210 women in the Cu-IUD cohort and 59 women in the LNG-IUS cohort who had a positive HPV lab test. After adjustment with propensity score matching, the magnitude standard deviation of the mean between these groups was less than 0.06.

7. General: cases per 1000 years is cited multiple times in the text. Should be "cases per 1000 person-

years"

Thank you for bringing this to our attention. We have revised the manuscript in the abstract (line 112-121) and results (lines 304 and 319) sections as well as the tables (lines 565-566 and 609-610).

8. lines 286-288: I suspect that there is insufficient data to allow sufficient stats power to compare the slopes at various time points, but if the Authors want to perform that formal analysis, then should include. Otherwise, the observation of changing slope has no statistical basis and should be omitted from discussion. Suffice to say that the two curves were/were not statistically divergent.

We agree that this kind of statistical analysis can not be done formally. We have updated the text to clarify that we are observing this by inspection (line 324).

9. lines 292-295: Should validate a larger random sample to verify that women generally (with or without neoplasms) were allocated correctly into Cu-IUD vs LNG-IUS categories, since mis allocation would affect the incidence rates.

Thank you for helping us determine the appropriate number of patients to sample. We have reviewed the charts of another 25 patients from the LNG-IUS cohort and 39 patients from the Cu-IUD cohort and found that the misclassification statistics were similarly low (lines 330-334).

10. lines 295-296: What were the results of analysis if limited to "retrievable biopsy confirmation"?

Thank you for interest in our validation process. We can not measure outcomes other than by using data in our database. In our main analysis, a cervical neoplasm outcome was indicated by a condition code that corresponded with the disease. To validate the accuracy of that method for identifying patients, under institutional IRB approval, we extracted data from an identified database and did a comparison between the condition codes and biopsy diagnoses and these agreed with each other. No changes to text.

Beta	Covariates
-0.55	age group: 15-19
-0.33	measurement during day -365 through 0 days relative to index: Gas panel - Venous cord blood
0.3	measurement during day -365 through 0 days relative to index: Parvovirus B19 IgG Ab [Units/volume] in Serum by Immunoassay
0.27	procedure_occurrence during day -365 through 0 days relative to index: Radiologic examination, chest; single view, frontal
0.27	measurement during day -365 through 0 days relative to index: Child weight centiles – finding
-0.26	procedure_occurrence during day -30 through 0 days relative to index: Removal of intrauterine device
-0.25	condition_era group during day -365 through 0 days relative to index: Psychoactive substance use disorder
0.24	observation during day -365 through 0 days relative to index: Patient encounter procedure
-0.23	drug_era group during day -30 through 0 days relative to index: Corticosteroids, potent (group III)
-0.22	measurement during day -365 through 0 days relative to index: Neisseria gonorrhoeae rRNA [Presence] in Unspecified specimen by DNA probe
-0.2	procedure_occurrence during day -365 through 0 days relative to index: Removal of intrauterine device
-0.2	measurement during day -365 through 0 days relative to index: Basophils [#/volume] in Blood
-0.19	condition_era group during day -365 through 0 days relative to index: Pregnancy test positive
0.19	measurement below normal range during day -365 through 0 days relative to index: Creatinine serum/plasma
0.19	procedure_occurrence during day -365 through 0 days relative to index: Gynecologic examination
-0.18	measurement below normal range during day -365 through 0 days relative to index: Hematocrit
0.18	procedure_occurrence during day -365 through 0 days relative to index: Screening mammography, bilateral (2-view study of each breast), including computer-aided detection (cad) when performed
-0.18	measurement during day -365 through 0 days relative to index: Monocytes [#/volume] in Blood by Automated count
0.17	measurement during day -30 through 0 days relative to index: Respiratory rate
-0.17	condition_era group during day -365 through 0 days relative to index: Pregnancy test negative

-0.17	drug_era group during day 0 through 0 days relative to index: ALIMENTARY TRACT AND METABOLISM
0.16	procedure_occurrence during day -365 through 0 days relative to index: Vaginal delivery only (with or without episiotomy and/or forceps)
-0.16	measurement during day -30 through 0 days relative to index: BP systolic
0.16	procedure_occurrence during day -30 through 0 days relative to index: Education about oral contraception
0.15	procedure_occurrence during day -365 through 0 days relative to index: Human immunodeficiency virus counseling
-0.15	drug_era group during day -365 through 0 days relative to index: Other antihistamines for systemic use
0.15	measurement during day -365 through 0 days relative to index: Body weight Stated
0.15	procedure_occurrence during day -365 through 0 days relative to index: Office or other outpatient visit for the evaluation and management of an established patient, which requires at least 2 of these 3 key components: An expanded problem focused history; An expanded problem focused examination; Medical decision making of low
-0.15	drug_era group during day 0 through 0 days relative to index: MUSCULO-SKELETAL SYSTEM
-0.14	measurement during day -365 through 0 days relative to index: BP diastolic
-0.14	procedure_occurrence during day -365 through 0 days relative to index: Office or other outpatient visit for the evaluation and management of a new patient, which requires these 3 key components: A detailed history; A detailed examination; Medical decision making of low complexity. Counseling and/or coordination of care with
-0.13	measurement during day -365 through 0 days relative to index: BP systolic
0.13	measurement within normal range during day -365 through 0 days relative to index: Hemoglobin
-0.13	measurement during day -365 through 0 days relative to index: Iron [Mass/volume] in Serum or Plasma
-0.12	measurement within normal range during day -365 through 0 days relative to index: Phosphate
-0.12	drug_era group during day -365 through 0 days relative to index: ANTIINFECTIVES FOR SYSTEMIC USE
-0.12	observation during day -365 through 0 days relative to index: H/O: food allergy
0.12	measurement within normal range during day -365 through 0 days relative to index: Erythrocyte mean corpuscular hemoglobin [Entitic mass] by Automated count
0.12	measurement during day -365 through 0 days relative to index: Hemoglobin
-0.12	measurement below normal range during day -365 through 0 days relative to index: Platelet count
-0.12	drug_era group during day -30 through 0 days relative to index: ESTROGENS
-0.11	condition_era group during day -365 through 0 days relative to index: Pain of head and neck region

0.11	drug_era group during day -365 through 0 days relative to index: DRUGS FOR CONSTIPATION
-0.11	measurement during day -365 through 0 days relative to index: Body height
-0.11	measurement within normal range during day -365 through 0 days relative to index: Bicarbonate [Moles/volume] in Serum
0.11	procedure_occurrence during day -365 through 0 days relative to index: Level IV - Surgical pathology, gross and microscopic examination Abortion - spontaneous/missed Artery, biopsy Bone marrow, biopsy Bone exostosis Brain/meninges, other than for tumor resection Breast, biopsy, not requiring microscopic evaluation of surgica
0.11	measurement during day -365 through 0 days relative to index: Choriogonadotropin.beta subunit free [Units/volume] in Serum or Plasma
-0.11	race = Black or African American
0.1	measurement within normal range during day -365 through 0 days relative to index: Calcium serum/plasma serum/plasma
-0.1	drug_era group during day 0 through 0 days relative to index: SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM
-0.1	measurement during day -365 through 0 days relative to index: Cholesterol.total/Cholesterol in HDL [Mass Ratio] in Serum or Plasma
-0.1	procedure_occurrence during day -365 through 0 days relative to index: Tetanus, diphtheria toxoids and acellular pertussis vaccine (Tdap), when administered to individuals 7 years or older, for intramuscular use
0.1	drug_era group during day -365 through 0 days relative to index: Corticosteroids, moderately potent (group II)
-0.1	drug_era group during day 0 through 0 days relative to index: DRUGS FOR PEPTIC ULCER AND GASTRO-OESOPHAGEAL REFLUX DISEASE (GORD)
0.1	condition_era group during day -365 through 0 days relative to index: Uterine scar from previous surgery in pregnancy, childbirth and the puerperium
-0.1	drug_era group during day -30 through 0 days relative to index: ANTIINFECTIVES FOR SYSTEMIC USE
0.1	observation during day -365 through 0 days relative to index: Routine antenatal care
-0.1	drug_era group during day -365 through 0 days relative to index: ANTIBACTERIALS FOR SYSTEMIC USE
0.09	observation during day -365 through 0 days relative to index: Postpartum care
0.09	observation during day -365 through 0 days relative to index: Contraception
0.09	measurement during day -365 through 0 days relative to index: Hepatitis B virus surface Ag [Presence] in Serum
-0.09	drug_era group during day -365 through 0 days relative to index: ENDOCRINE THERAPY
-0.09	condition_era group during day -365 through 0 days relative to index: Threatened miscarriage
0.09	condition_era group during day -365 through 0 days relative to index: Infectious disease in mother complicating pregnancy, childbirth AND/OR puerperium

0.09	measurement during day -30 through 0 days relative to index: Hemoglobin
0.08	drug_era group during day -365 through 0 days relative to index: Cephalexin
-0.08	drug_era group during day -30 through 0 days relative to index: MUSCULO-SKELETAL SYSTEM
0.07	measurement during day -30 through 0 days relative to index: Body temperature
-0.07	measurement during day -365 through 0 days relative to index: Rubella virus IgG Ab [Presence] in Serum
0.07	drug_era group during day -365 through 0 days relative to index: sodium citrate
0.07	measurement within normal range during day -365 through 0 days relative to index: Hemoglobin A/Hemoglobin.total in Blood by Electrophoresis
-0.07	observation during day -365 through 0 days relative to index: Tobacco smoking behavior - finding
-0.07	measurement during day -365 through 0 days relative to index: Appearance of Urine
0.07	drug_era group during day -365 through 0 days relative to index: ANTIPRURITICS, INCL. ANTIHISTAMINES, ANESTHETICS, ETC.
-0.07	measurement during day -365 through 0 days relative to index: HIV 1+2 Ab+HIV1 p24 Ag [Presence] in Serum or Plasma by Immunoassay
0.07	measurement during day -365 through 0 days relative to index: Hemoglobin A1c (Glycated)
0.07	measurement above normal range during day -365 through 0 days relative to index: Alkaline phosphatase serum/plasma
0.07	observation during day -365 through 0 days relative to index: Oral contraception
-0.06	measurement during day -365 through 0 days relative to index: Streptococcus agalactiae DNA [Presence] in Unspecified specimen by Probe and target amplification method
0.06	procedure_occurrence during day -30 through 0 days relative to index: Gynecologic examination
-0.06	drug_era group during day -30 through 0 days relative to index: NERVOUS SYSTEM
0.06	condition_era group during day -365 through 0 days relative to index: Female reproductive system disorder
0.06	measurement during day -365 through 0 days relative to index: Bacteria identified in Urine by Culture
-0.06	procedure_occurrence during day -365 through 0 days relative to index: Urine pregnancy test, by visual color comparison methods
0.06	condition_era group during day -365 through 0 days relative to index: Dizziness
-0.06	observation during day -365 through 0 days relative to index: Emergency contraception
0.06	measurement during day -30 through 0 days relative to index: Heart rate
0.05	condition_era group during day -365 through 0 days relative to index: Mycosis

-0.05	measurement during day -30 through 0 days relative to index: Body mass index
0.05	condition_era group during day -365 through 0 days relative to index: Distention of blood vessel
0.05	drug_era group during day 0 through 0 days relative to index: Softeners, emollients
0.05	procedure_occurrence during day -365 through 0 days relative to index: Cytopathology, cervical or vaginal (any reporting system), collected in preservative fluid, automated thin layer preparation; with screening by automated system and manual rescreening or review, under physician supervision
0.05	condition_era group during day -365 through 0 days relative to index: Dizziness and giddiness
-0.05	condition_era group during day -365 through 0 days relative to index: Mood disorder
0.05	drug_era group during day -365 through 0 days relative to index: Enemas
-0.05	condition_era group during day -365 through 0 days relative to index: Patient currently pregnant
0.05	measurement during day -365 through 0 days relative to index: Blood group antibody screen [Presence] in Serum or Plasma
-0.05	condition_era group during day -365 through 0 days relative to index: Neoplastic disease
-0.05	condition_era group during day -365 through 0 days relative to index: Inflammatory disorder of musculoskeletal system
0.05	age group: 40-44
0.05	observation during day -30 through 0 days relative to index: Postpartum care
0.05	measurement within normal range during day -365 through 0 days relative to index: Erythrocyte distribution width [Ratio] by Automated count
-0.04	measurement during day -365 through 0 days relative to index: Urobilinogen [Units/volume] in Urine by Test strip
0.04	drug_era group during day -365 through 0 days relative to index: Folic acid and derivatives
0.04	drug_era group during day -365 through 0 days relative to index: Latex
-0.04	condition_era group during day -365 through 0 days relative to index: Mass of trunk
0.04	drug_era group during day -365 through 0 days relative to index: Folic Acid
0.04	observation during day -30 through 0 days relative to index: Tobacco smoking behavior - finding
-0.04	measurement within normal range during day -365 through 0 days relative to index: Triglyceride [Mass/volume] in Serum or Plasma
-0.04	measurement during day -365 through 0 days relative to index: Finding of rate of respiration
0.04	drug_era group during day -365 through 0 days relative to index: Ibuprofen
-0.04	condition_era group during day -365 through 0 days relative to index: Unwanted pregnancy

0.04	drug_era group during day -365 through 0 days relative to index: DERMATOLOGICALS
-0.04	measurement below normal range during day -365 through 0 days relative to index: Glucose lab
-0.04	drug_era group during day -30 through 0 days relative to index: Ethinyl Estradiol
0.03	measurement within normal range during day -365 through 0 days relative to index: Erythrocyte mean corpuscular volume [Entitic volume] by Automated count
-0.03	measurement above normal range during day -365 through 0 days relative to index: Leukocytes [#/volume] in Blood by Automated count
-0.03	condition_era group during day -365 through 0 days relative to index: Excessive and frequent menstruation
0.03	condition_era group during day -365 through 0 days relative to index: Vulvitis
0.03	drug_era group during day -365 through 0 days relative to index: Iron bivalent, oral preparations
-0.03	measurement during day -30 through 0 days relative to index: Body surface area
-0.03	measurement during day -365 through 0 days relative to index: Gas panel - Arterial cord blood
-0.03	drug_era group during day -365 through 0 days relative to index: BETA-LACTAM ANTIBACTERIALS, PENICILLINS
-0.03	measurement during day -365 through 0 days relative to index: Cholesterol [Mass/volume] in Serum or Plasma
0.03	measurement during day -365 through 0 days relative to index: Body weight Measured
-0.03	ethnicity = Hispanic or Latino
-0.03	drug_era group during day -30 through 0 days relative to index: DERMATOLOGICALS
0.03	drug_era group during day -365 through 0 days relative to index: SENSORY ORGANS
0.03	drug_era group during day -365 through 0 days relative to index: TOPICAL PRODUCTS FOR JOINT AND MUSCULAR PAIN
0.03	condition_era group during day -365 through 0 days relative to index: Symptomatic disorders in pregnancy
-0.03	measurement during day -30 through 0 days relative to index: Body height
0.03	drug_era group during day 0 through 0 days relative to index: Ondansetron
-0.03	measurement during day -30 through 0 days relative to index: Neisseria gonorrhoeae rRNA [Presence] in Unspecified specimen by DNA probe
0.03	measurement below normal range during day -365 through 0 days relative to index: Total Bilirubin serum/plasma
-0.03	drug_era group during day -30 through 0 days relative to index: SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM
-0.02	procedure_occurrence during day -365 through 0 days relative to index: Office or other outpatient visit for the evaluation and management of a new patient, which requires these 3 key components: A comprehensive history; A

	comprehensive examination; Medical decision making of moderate complexity. Counseling and/or coordinatio
-0.02	drug_era group during day -365 through 0 days relative to index: GENITO URINARY SYSTEM AND SEX HORMONES
-0.02	condition_era group during day -365 through 0 days relative to index: Leiomyoma
-0.02	index year: 2012
-0.02	drug_era group during day -365 through 0 days relative to index: PSYCHOLEPTICS
-0.02	procedure_occurrence during day -365 through 0 days relative to index: Injection or infusion of other therapeutic or prophylactic substance
0.02	measurement during day -365 through 0 days relative to index: Reagin Ab [Presence] in Serum by RPR
0.02	observation during day -365 through 0 days relative to index: Requires vaccination
0.01	condition_era group during day -365 through 0 days relative to index: Finding related to pregnancy
-0.01	condition_era group during day -365 through 0 days relative to index: Urinary tract infectious disease
-0.01	condition_era group during day -365 through 0 days relative to index: Acute inflammatory disease
-0.01	procedure_occurrence during day -365 through 0 days relative to index: Office or other outpatient visit for the evaluation and management of an established patient, which requires at least 2 of these 3 key components: A problem focused history; A problem focused examination; Straightforward medical decision making. Counselin
-0.01	procedure_occurrence during day -365 through 0 days relative to index: Ultrasound, pregnant uterus, real time with image documentation, first trimester fetal nuchal translucency measurement, transabdominal or transvaginal approach; single or first gestation
-0.01	condition_era group during day -365 through 0 days relative to index: Inflammation of specific body systems
-0.01	condition_era group during day -365 through 0 days relative to index: Gestation period, 12 weeks
-0.01	drug_era group during day -365 through 0 days relative to index: Antiinfectives and antiseptics for local oral treatment
0.01	index year: 2018
-0.01	drug_era group during day -365 through 0 days relative to index: Morphine
0.01	condition_era group during day -365 through 0 days relative to index: Drug dependence
-0.01	drug_era group during day -30 through 0 days relative to index: VITAMINS
0.01	drug_era group during day -365 through 0 days relative to index: Iron Carbonyl
0.01	procedure_occurrence during day -365 through 0 days relative to index: Hemoglobin fractionation and quantitation; electrophoresis (eg, A2, S, C, and/or F)

-0.01	measurement during day -30 through 0 days relative to index: Immature granulocytes [#/volume] in Blood
0.01	age group: 30-34
0.01	drug_era group during day -365 through 0 days relative to index: DRUGS FOR CONSTIPATION
-0.01	measurement above normal range during day -365 through 0 days relative to index: Erythrocyte mean corpuscular hemoglobin [Entitic mass] by Automated count
0.01	condition_era group during day -365 through 0 days relative to index: Low back pain
-0.01	condition_era group during day -365 through 0 days relative to index: Menstruation absent
-0.01	race = White

Supplementary Table 1: A representative group of variables in the propensity model with associated coefficients.

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 choose to OPT-IN

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. In order for an administrative database study to be considered for publication in Obstetrics & Gynecology, the database used must be shown to be reliable and validated. In your response, please tell us who entered the data and how the accuracy of the database was validated. This same information should be included in the Materials and Methods section of the manuscript.

4. Responsible reporting of research studies, which includes a complete, transparent, accurate and

timely account of what was done and what was found during a research study, is an integral part of good research and publication practice and not an optional extra. Obstetrics & Gynecology supports initiatives aimed at improving the reporting of health research, and we ask authors to follow specific guidelines for reporting randomized controlled trials (ie, CONSORT), observational studies (ie, STROBE), meta-analyses and systematic reviews of randomized controlled trials (ie, PRISMA), harms in systematic reviews (ie, PRISMA for harms), studies of diagnostic accuracy (ie, STARD), meta-analyses and systematic reviews of observational studies (ie, MOOSE), economic evaluations of health interventions (ie, CHEERS), quality improvement in health care studies (ie, SQUIRE 2.0), and studies reporting results of Internet e-surveys (CHERRIES). Include the appropriate checklist for your manuscript type upon submission. Please write or insert the page numbers where each item appears in the margin of the checklist. Further information and links to the checklists are available at https://urldefense.proofpoint.com/v2/url?u=http-3A__ong.editorialmanager.com&d=DwIGaQ&c=G2MiLlal7SXE3PeSnG8W6_JBU6FcdVjSsBSbw6gcRoU&r=6ocU1xgyteeU3sh3v-LKG7Cr4lqXU6phMbh5npNM86c&m=O77x9f9Ljka3tEIdqklZ1TIXUW8-TZvj-N5BoK7eEAA&s=kcE0-Z8F_3N69YSww3x1vJLCOqeIDeXXUvxDWzpAJYQ&e= . In your cover letter, be sure to indicate that you have followed the CONSORT, MOOSE, PRISMA, PRISMA for harms, STARD, STROBE, CHEERS, SQUIRE 2.0, or CHERRIES guidelines, as appropriate.

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://urldefense.proofpoint.com/v2/url?u=https-3A__www.acog.org_About-2DACOG_ACOG-2DDepartments_Patient-2DSafety-2Dand-2DQuality-2DImprovement_reVITALize&d=DwIGaQ&c=G2MiLlal7SXE3PeSnG8W6_JBU6FcdVjSsBSbw6gcRoU&r=6ocU1xgyteeU3sh3v-LKG7Cr4lqXU6phMbh5npNM86c&m=O77x9f9Ljka3tEIdqklZ1TIXUW8-TZvj-N5BoK7eEAA&s=Y9gCG8OPWj9jqgvokcepJb25qrwbgSUo6s7omuVbSR8&e= . 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, references, 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. Only standard abbreviations and acronyms are allowed. A selected list is available online at https://urldefense.proofpoint.com/v2/url?u=http-3A__edmgr.ovid.com_ong_accounts_abbreviations.pdf&d=DwIGaQ&c=G2MiLlal7SXE3PeSnG8W6_JBU6FcdVjSsBSbw6gcRoU&r=6ocU1xgyteeU3sh3v-LKG7Cr4lqXU6phMbh5npNM86c&m=O77x9f9Ljka3tEIdqklZ1TIXUW8-TZvj-N5BoK7eEAA&s=CoJ90p0YdyG3yIRLoJ8fcq2w6BZawVOuco_yNX6j7Sc&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.

10. 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.

11. 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%").

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:https://urldefense.proofpoint.com/v2/url?u=http-3A__edmgr.ovid.com_ong_accounts_table-5Fchecklist.pdf&d=DwIGaQ&c=G2MiLlal7SXE3PeSnG8W6_JBU6FcdVjSsBSbw6gcRoU&r=6ocU1xgyteeU3sh3v-LKG7Cr4lqXU6phMbh5npNM86c&m=O77x9f9Ljka3tEIdqklZ1TIXUW8-TZvj-N5BoK7eEAA&s=bCzlXQNO_3jezRmLNJLZ-61ni1t9zUJSKVUc4lPXogQ&e= .

13. The Journal's Production Editor had the following to say about the figures in your manuscript:

"Figure 1: Please upload as a figure file on Editorial Manager."

When you submit your revision, art saved in a digital format should accompany it. If your figure was created in Microsoft Word, Microsoft Excel, or Microsoft PowerPoint formats, please submit your original source file. Image files should not be copied and pasted into Microsoft Word or Microsoft PowerPoint.

When you submit your revision, art saved in a digital format should accompany it. Please upload each figure as a separate file to Editorial Manager (do not embed the figure in your manuscript file).

If the figures were created using a statistical program (eg, STATA, SPSS, SAS), please submit PDF or EPS files generated directly from the statistical program.

Figures should be saved as high-resolution TIFF files. The minimum requirements for resolution are 300 dpi for color or black and white photographs, and 600 dpi for images containing a photograph with text labeling or thin lines.

Art that is low resolution, digitized, adapted from slides, or downloaded from the Internet may not reproduce.

14. Authors whose manuscripts have been accepted for publication have the option to pay an article processing charge and publish open access. With this choice, articles are made freely available online immediately upon publication. An information sheet is available at https://urldefense.proofpoint.com/v2/url?u=http-3A__links.lww.com_LWW-2DES_A48&d=DwIGaQ&c=G2MiLlal7SXE3PeSnG8W6_JBU6FcdVjSsBSbw6gcRoU&r=6ocU1xgyteeU3sh3v-LKG7Cr4lqXU6phMbh5npNM86c&m=O77x9f9Ljka3tEIdqklZ1TIXUW8-TZvj-N5BoK7eEAA&s=HmBMIB9iHuEBfuUT_loOa9aPZuj-l8OKWQvndfF6dsc&e= . The cost for publishing an article as open access can be found at https://urldefense.proofpoint.com/v2/url?u=http-3A__edmgr.ovid.com_acd_accounts_ifauth.htm&d=DwIGaQ&c=G2MiLlal7SXE3PeSnG8W6_JBU6FcdVjSsBSbw6gcRoU&r=6ocU1xgyteeU3sh3v-LKG7Cr4lqXU6phMbh5npNM86c&m=O77x9f9Ljka3tEIdqklZ1TIXUW8-TZvj-N5BoK7eEAA&s=WZHyb3SL3Z6Amywq5DOZVK5hxm8C5b98yqnYZYMng4U&e= .

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

***

If you choose to revise your manuscript, please submit your revision through Editorial Manager at https://urldefense.proofpoint.com/v2/url?u=http-3A__ong.editorialmanager.com&d=DwIGaQ&c=G2MiLlal7SXE3PeSnG8W6_JBU6FcdVjSsBSbw6gcRoU&r=6ocU1xgyteeU3sh3v-LKG7Cr4lqXU6phMbh5npNM86c&m=O77x9f9Ljka3tEIdqklZ1TIXUW8-TZvj-N5BoK7eEAA&s=kcEo-Z8F_3N69YSww3x1vJLCOqeIDeXXUvxDWzpAJYQ&e= . 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 (https://urldefense.proofpoint.com/v2/url?u=http-3A__edmgr.ovid.com_ong_accounts_authors.pdf&d=DwIGaQ&c=G2MiLlal7SXE3PeSnG8W6_JBU6FcdVjSsBSbw6gcRoU&r=6ocU1xgyteeU3sh3v-LKG7Cr4lqXU6phMbh5npNM86c&m=O77x9f9Ljka3tEIdqklZ1TIXUW8-TZvj-N5BoK7eEAA&s=fwnCSZ3mz1YZ2FdskEkUKiS76xnNVd25sOl-J-AERt4&e=), and
* A point-by-point response to each of the received comments in this letter.

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

Again, your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Oct 14, 2019, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

The Editors of Obstetrics & Gynecology

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