OBSTETRICS & GYNECOLOGY

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

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

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

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

Date: May 07, 2019
To: "Tina Raine-Bennett" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-19-698

RE: Manuscript Number ONG-19-698

Depot medroxyprogesterone Acetate, Oral Contraceptive, and Intrauterine Device Use and Fracture Risk

Dear Dr. Raine-Bennett:

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

REVIEWER COMMENTS:

Reviewer #1:

The following are suggestions for improvements:

Abstract

The results as stated are inaccurate because the results are flipped in Table 4. DMPA recent use more than 2 years should have a fracture rate/1000 person-years of 6.1 and past use 2 years or less should have a fracture rate/100 person-years of 7.8-at least this is by the fractures and person-years as listed. This change will then alter your results as reported and your hazard ratios.

Introduction

1. Your specifically list as your stated goal (line 84) assessing fracture risk in adolescents but these are not specifically addressed in your results section. In addition, the reference of ages 12-45 (line 87) does not match the table 3 data listing ages "50 and older"

Methodology

2. Lines 93-94-please provide further details regarding data extraction-who were the staff performing and in what manner

3. It is evident that a lot of time and thought went into defining the exposure (contraceptive use) but in lines 137-148, please further explain the chart extraction process for the outcome (Fractures) in question. It is difficult to imagine that over 7,000 fractures in women of reproductive age are all fragility fractures. Were there AIS evaluations performed quantifying severity of injury in addition to the ICD-9 codes listed? If not, why not-is this information not available?

4. In your list of confounders (lines 152-161, was rheumatoid arthritis, hyperthyroidism, or inhaled corticosteroids for asthma taken into consideration?

5. Lines 215-218 and lines 224-227 as well as discussion of these results will need to be changed based on correction of data in Table 4

6. Please include some of the above mentioned information as further details of limitations with respect to likely overestimation of fragility fractures

Reviewer #2: Manuscript ONG-19-698

Summary: This large retrospective cohort study provides important US population-based data regarding the risk of fracture in individuals who have used depo-provera, OCPs, POPs, or IUS. While the FDA has placed a black box warning on using depo-provera for >2 years due to concerns about fracture risk, there is a paucity of substantive, high-quality data to inform patients and providers regarding the true risk of fracture as it relates to depo-provera and these other methods. This is a very well executed and written study and will be an important contribution to the literature.

Title page:

1. Lines 4-5: Please note the superscript "a" for both authors - please correct with the corresponding number for each author's affiliation.

Abstract:

1. Please specify the age range of the study population in the abstract.

2. Line 57: Please change "omen" to "women.

Introduction:

1. I recommend explaining how the black box warning can be a barrier to some individuals continuing with a method that otherwise works well for them due to some providers' discomfort with going against the warning - the implications of the warning.

2. Line 89: This is a bit confusing - do you mean that you hypothesize that depo-provera would not have increased risk of fracture compared to OCP or IUD use or that OCP and IUDs would not have increased risk of fracture compared to non-users of those methods?

Methods:

1. Lines Line 91: I recommend stating that the age range is the age at the index date or wait to include the age information lower down when you explain the definition of the index date. Otherwise it leaves the reader wondering at what point are these participants 12-45 years.

2. Line 92: Please specify here that you include LNG IUDs and Copper IUDs. This information appears in the discussion, but should be included here as well.

3. Paragraph starting line 152: Please explain how you determined which variables to include as potential confounders - based on what was available in the chart? Literature review? Why not include prior pregnancies and h/o breast feeding?

Results:
1. N/A

Discussion:

1. Lines 288-91: Please elaborate - biological plausibility about what? It seems that this thought was a bit truncated.

2. Line 292: I would recommend stating "potential risks on bone health".

3. As stated in the comments in the introduction, I recommend commenting on how the black box warning can be an impediment to some individuals continuing on a method of contraception that is working very well for them. Perhaps introduce the idea of shared decision making in contraceptive counseling here. Contraceptive counseling is a discussion about risks and benefit and determining what is in the best interest of the patient. While there may be some additional risk of fracture with depo-provera, this additional risk is overall small and should not be regarded as an absolute contraindication to continuing depo-provera with patients who desire to continue the method after an open discussion about this potential risk.

Reviewer #3: Overall Comments: The authors presents the results of a retrospective cohort study assessing fracture risks among adolescents and pre-menopausal women who used depot medroxyprogesterone acetate (DMPA), oral contraception (combined and progestin only), or intrauterine devices (IUD) at a large health care delivery system. The hypothesis was that risk fracture would be increased among women with DMPA use. This is a large patient population and inclusions/exclusions were well described. Overall, this paper is a robust addition to the DMPA literature regarding fracture

risk even though retrospective in nature. Findings are consistent with current ACOG guidelines. Specific comments below.

Specific Comments:

Title: good

Short title: good

Précis: OK

Abstract: Please write Methods from 3rd person perspective-too many "We's". Line 57, add "w" to "omen". Overall good summary of the results.

Introduction: Provides good rationale for the study.

Materials and Methods: Well described.

Results: Could consider shortening lines 182-186 as well described on Figure 1. What was the mean and median, range of women sustaining fractures?

Discussion: Thoughtful discussion of the data and alignment with the current literature. Impactful as reflects a large pharmacy database linked to clinical data. Limitations noted.

Tables/Figures: Good

STATISTICAL EDITOR'S COMMENTS:

1. lines 137-151: If a woman had more than one fracture during the study period, how were those data analyzed? That is, there could be some increased risk of subsequent fracture and those should not be counted as independent events. How many women had > 1 fracture?

2. Table 1: Were there any statistical differences in the follow-up time for the various subsets by contraceptive type? Was the frequency of prior fracture statistically different by contraceptive method? Since the group with prior fractures have a higher risk of recurrence, should do sensitivity analysis to verify whether the association of fracture risk vs DMPA still would hold if those women with prior fractures were excluded. Need units for BMI.

3. Table 3: Need units for BMI. The absolute count for # fractures associated with epilepsy (n = 35) or with corticosteroid use (n = 4) are too few to allow for adjustment with multiple covariates in the aHR model.

4, Table 4: Too few instances (n = 6) fractures among > 2 yr past users of DMPA to allow for multiple adjustment of aHR model.
Again, should employ sensitivity analysis to corroborate the association of DMPA use with fracture occurrence.

5. General: Given the large data set and large number of cases of fracture, should corroborate the multivariate adjustment by comparing the fracture cases with matched controls, matching on all identified risk factors (except contraceptive type). This would provide more evidence of an association of DMPA use with fracture risk, although unidentified confounders could not be excluded as a cause, since the study was not randomized.

ASSOCIATE EDITOR - GYN

Please start the Abstract Conclusion with a more dynamic, meaningful opening statement

EDITORIAL OFFICE COMMENTS:

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

2. As of December 17, 2018, Obstetrics & Gynecology has implemented an "electronic Copyright Transfer Agreement" (eCTA) and will no longer be collecting author agreement forms. When you are ready to revise your manuscript, you will

be prompted in Editorial Manager (EM) to click on "Revise Submission." Doing so will launch the resubmission process, and you will be walked through the various questions that comprise the eCTA. Each of your coauthors will receive an email from the system requesting that they review and electronically sign the eCTA.

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

3. 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. Provide a précis on the second page, for use in the Table of Contents. The précis is a single sentence of no more than 25 words that states the conclusion(s) of the report (ie, the bottom line). The précis should be similar to the abstract's conclusion. Do not use commercial names, abbreviations, or acronyms in the précis. Please avoid phrases like "This paper presents" or "This case presents."

9. The most common deficiency in revised manuscripts involves the abstract. Be sure there are no inconsistencies between the Abstract and the manuscript, and that the Abstract has a clear conclusion statement based on the results found in the paper. Make sure that the abstract does not contain information that does not appear in the body text. If you submit a revision, please check the abstract carefully.

In addition, the abstract length should follow journal guidelines. The word limits for different article types are as follows: Original Research articles, 300 words. Please provide a word count.

10. Only standard abbreviations and acronyms are allowed. A selected list is available online at http://edmgr.ovid.com/ong/accounts/abbreviations.pdf. Abbreviations and acronyms cannot be used in the title or précis. Abbreviations and acronyms must be spelled out the first time they are used in the abstract and again in the body of the manuscript.

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

12. We discourage claims of first reports since they are often difficult to prove. How do you know this is the first report? If this is based on a systematic search of the literature, that search should be described in the text (search engine, search terms, date range of search, and languages encompassed by the search). If on the other hand, it is not based on a systematic search but only on your level of awareness, it is not a claim we permit.

13. Please review the journal's Table Checklist to make sure that your tables conform to journal style. The Table Checklist is available online here: http://edmgr.ovid.com/ong/accounts/table_checklist.pdf.

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

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

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

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

Again, your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by May 28, 2019, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

The Editors of Obstetrics & Gynecology

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

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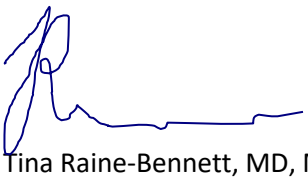
June 3, 2019

The Editors of Obstetrics & Gynecology
RE: Manuscript Number ONG-19-698
Depot medroxyprogesterone Acetate, Oral Contraceptive, and Intrauterine Device Use and Fracture Risk

Dear Editors,
Thank you for your thoughtful review of our manuscript and consideration for publication in Obstetrics and Gynecology. We have studied the reports submitted by the referees and respond to each comment below in italic. All references to line numbers below refer to the line numbers in the original manuscript that was submitted. Changes in the revised manuscript are indicated as tracked changes; we are submitting a REVISED draft with tracked changes and a clean draft without tracked changes.



Tina Raine-Bennett, MD, MPH
[redacted]

REVIEWER COMMENTS:

Reviewer #1:

Abstract
The results as stated are inaccurate because the results are flipped in Table 4. DMPA recent use more than 2 years should have a fracture rate/1000 person-years of 6.1 and past use 2 years or less should have a fracture rate/100 person-years of 7.8-at least this is by the fractures and person-years as listed. This change will then alter your results as reported and your hazard ratios.

The reviewer is correct the results are flipped in Table 4; however, only the number of fractures and person-years for DMPA recent use of more than 2 years were switched with the number of fractures and person-years for DMA past use two years. The fracture rates are NOT flipped; they are correct. So the abstract is correct; the number of fractures and person-years in Table 4 have been corrected. We have also re-checked all numbers in all the tables.

Introduction

1. Your specifically list as your stated goal (line 84) assessing fracture risk in adolescents but these are not specifically addressed in your results section. In addition, the reference of ages 12-45 (line 87) does not match the table 3 data listing ages "50 and older"

Table 3 provides data for women by age at the outcome. Women were eligible for the study if they received a DMPA shot at age 12-45 from 2005 to 2015, however they were followed for potentially up to 12 years (2005 to 2017) so fractures could have occurred over age 50. We edited the header in Table 3 to state "age at outcome". We also added age categories at entry to Table 1 to highlight method use by age categories which includes adolescents. We added information about the proportion DMPA users who were adolescents and fracture rates for adolescents to the results section and highlighted the number of adolescents in the discussion. We have also changed line 87 to state "women of reproductive age" to be less confusing with later text as this is the population of interest that uses contraception.

Methodology

2. Lines 93-94-please provide further details regarding data extraction-who were the staff performing and in what manner

The text was edited to note that the data was abstracted by the second author (MC) and we provided more information about the research databases maintained in the Division of Research at Kaiser. We think it is beyond the scope of the paper to describe the "manner" in which data is extracted which (in short) involves use of SAS programs running SQL extracts of Oracle tables using extract, transform, and load (ETL) procedures to produce SAS datasets.

3. It is evident that a lot of time and thought went into defining the exposure (contraceptive use) but in lines 137-148, please further explain the chart extraction process for the outcome (Fractures) in question. It is difficult to imagine that over 7,000 fractures in women of reproductive age are all fragility fractures.

The text in lines 137-151 has been edited and rearranged to clarify the approach for identifying non-traumatic (fragility) fractures, which was accomplished by selection of specific fracture sites identified in specific departments and exclusion of fractures associated with major trauma. The number of non-traumatic fractures in this large database was large, making clinical adjudication in each case time-prohibited. We have noted this in the methods section and listed this as a limitation of the study.

Were there AIS evaluations performed quantifying severity of injury in addition to the ICD-9 codes listed? If not, why not-is this information not available?

Injury scoring or the Abbreviated Injury Scale (AIS) evaluation was not performed as these are designed to predict trauma patient outcomes, which is not relevant for this study.

4. In your list of confounders (lines 152-161, was rheumatoid arthritis, hyperthyroidism, or inhaled corticosteroids for asthma taken into consideration?

We did not control for rheumatoid arthritis per se, only corticosteroid use for treatment, or control for hyperthyroidism; we have added text to the discussion section under limitations to note that we did not control for all potential confounders such as these which occur less commonly. We did not include inhaled steroids as It is difficult to quantify dose of inhaled steroids received and there is less risk of systemic effects. The text in the methods section has been edited to note that we considered "oral" steroid therapy.

5. Lines 215-218 and lines 224-227 as well as discussion of these results will need to be changed based on correction of data in Table 4

See response to comment #1, Table 4 has been corrected; the results and interpretation of results do not need to be revised.

6. Please include some of the above mentioned information as further details of limitations with respect to likely overestimation of fragility fractures

Text has been added to the discussion of limitations to indicate that we did not perform clinical adjudication for all fractures.

Reviewer #2: Manuscript ONG-19-698
Title page:
1. Lines 4-5: Please note the superscript "a" for both authors - please correct with the corresponding number for each author's affiliation.

The superscripts have been corrected to "1".

Abstract:
1. Please specify the age range of the study population in the abstract.

The age range for the study population has been added to the abstract.

2. Line 57: Please change "omen" to "women.

This correction has been made.

Introduction:
1. I recommend explaining how the black box warning can be a barrier to some individuals continuing with a method that otherwise works well for them due to some providers' discomfort with going against the warning - the implications of the warning.

Text in the first and second paragraph of the introduction have been rearranged and edited to make this point clearer.

2. Line 89: This is a bit confusing - do you mean that you hypothesize that depo-provera would not have increased risk of fracture compared to OCP or IUD use or that OCP and IUDs would not have increased risk of fracture compared to non-users of those methods?

The text has been clarified to state: "… hypothesized that fracture risk is increased with DMPA use compared to OCP and IUD use, while there is no increased risk for OCP use and IUD use compared to other method use."

Methods:
1. Lines 91: I recommend stating that the age range is the age at the index date or wait to include the age information lower down when you explain the definition of the index date. Otherwise it leaves the reader wondering at what point are these participants 12-45 years.

The text of line 91 has been edited to clarify that the study population included women who were age 12-45 and initiated the study methods. The first line of the next paragraph was eliminated as it was redundant

2. Line 92: Please specify here that you include LNG IUDs and Copper IUDs. This information appears in the discussion but should be included here as well.

The text has been edited to specify use of copper and levonorgestrel IUDs in the abstract, methods, results, and discussion sections.

3. Paragraph starting line 152: Please explain how you determined which variables to include as potential confounders - based on what was available in the chart? Literature review?

Potential confounders were based on known risk factors in the literature; this text was edited, and references noting association of the confounders with fracture risk were added.

Why not include prior pregnancies and h/o breast feeding?

While bone mineral density decreases transiently during and after pregnancy and lactation , prior pregnancy and history of lactation per se have not been shown to be associated with osteoporosis or fracture risk in the literature.

References:
Karlsson, C. Obrant, K. J. Karlsson, M. Pregnancy and lactation confer reversible bone loss in humans. Osteoporos Int. 2001;12:828-34.

Karlsson MK, Ahlborg HG, Karlsson C. Pregnancy and lactation are not risk factors for osteoporosis or fractures. Lakartidningen. 2005;102:290-3.

Results:
1. N/A

Discussion:

1. Lines 288-91: Please elaborate - biological plausibility about what? It seems that this thought was a bit truncated.

The text has been expanded to provide more clarity about how it could be biologically plausible to observe elevated risk with recent use, but not past use given the known reversibility of BMD changes seen with DMPA use.

2. Line 292: I would recommend stating "potential risks on bone health".

See below - this paragraph has been edited to note "risk….demonstrated in this study" rather than "potential" risk.

3. As stated in the comments in the introduction, I recommend commenting on how the black box warning can be an impediment to some individuals continuing on a method of contraception that

is working very well for them. Perhaps introduce the idea of shared decision making in contraceptive counseling here. Contraceptive counseling is a discussion about risks and benefit and determining what is in the best interest of the patient. While there may be some additional risk of fracture with depo-provera, this additional risk is overall small and should not be regarded as an absolute contraindication to continuing depo-provera with patients who desire to continue the method after an open discussion about this potential risk.

The last paragraph of the discussion has been edited to clearly state the implications of the study with regards to the black box warning and continuation of DMPA. Since we did not study shared-decision making per se in the study we state that risks and benefits should be considered in the decision making process.

Reviewer #3:

Abstract: Please write Methods from 3rd person perspective-too many "We's". Line 57, add "w" to "omen". Overall good summary of the results.

The abstract as well as introductory sentences to paragraphs in the methods and discussion section have been edited to be primarily from the 3rd person perspective.

Results: Could consider shortening lines 182-186 as well described on Figure 1.

Lines 182-187 have been shortened as suggested.

What was the mean and median, range of women sustaining fractures?

We have added the median age (standard deviation and range) of women with fractures to the text of the results.

STATISTICAL EDITOR'S COMMENTS:

1. lines 137-151: If a woman had more than one fracture during the study period, how were those data analyzed? That is, there could be some increased risk of subsequent fracture and those should not be counted as independent events. How many women had > 1 fracture?

We assessed "first fractures"; this was stated in line 137 of the original text. To make this clearer, a sentence was added to the analysis description: "Women were censored after the first fracture." We also added the word "incident" before the word "fracture" in the statement of the objectives in the introduction.

2. Table 1: Were there any statistical differences in the follow-up time for the various subsets by contraceptive type? Was the frequency of prior fracture statistically different by contraceptive method?

Table 1 is intended to be descriptive we are not testing hypotheses. Also with the large study numbers most differences are statistically significant.

Since the group with prior fractures have a higher risk of recurrence, should do sensitivity analysis to verify whether the association of fracture risk vs DMPA still would hold if those women with prior fractures were excluded.

See response to comment #3 below.

Need units for BMI.

The Units and cutoff for BMI categories have been added

3. Table 3: Need units for BMI. The absolute count for # fractures associated with epilepsy (n = 35) or with corticosteroid use (n = 4) are too few to allow for adjustment with multiple covariates in the aHR model.

We agree that the numbers of women with these risk factors and the number of fractures are too small to draw conclusions about these risk factors. We conducted sensitivity analyses: 1) removing women with corticosteroid use (n=49); 2) removing women with corticosteroid use or epilepsy (n= 818); 3) removing women with corticosteroid use, epilepsy, or prior fractures (n= 2,279) . Estimates of fracture risk for the contraceptive groups did not change in any of the analyses. The adjusted risk of fracture was the same for all DMPA and other contraceptive use categories. This is not surprising given the small numbers of women with these risk factors. We added a sentence to the methods about the sensitivity analyses and to the results section noting no differences between the main findings and those of the sensitivity analyses. The co-authors SA and MAS, both of whom are biostatisticians, feel strongly that the variables be left in the analysis and tables, as it is generally considered statistically appropriate to adjust for the effects of known risk factors in multivariable analyses even when the absolute outcome count is small for those subgroups. We also believe that readers will want to see that we controlled for known risk factors. However, since the objective of the study was to determine associations between contraceptive groups and fracture risk, not to confirm known risk factors, and given the large confidence intervals we have eliminated the text with risk estimates for known risk factors in the abstract. We now comment on those known risk factors in the text only to note how our findings seem consistent with other studies.

4, Table 4: Too few instances (n = 6) fractures among > 2 yr past users of DMPA to allow for multiple adjustment of aHR model. Again, should employ sensitivity analysis to corroborate the association of DMPA use with fracture occurrence.

While the number of fractures was small among this group and the confidence intervals are wider, we think it is important to keep this group in the model as they are central to the study objectives. We have strengthened the language in the discussion about interpretation of the risk estimate for this group given less observation time and the small number of fractures.

5. General: Given the large data set and large number of cases of fracture, should corroborate the multivariate adjustment by comparing the fracture cases with matched controls, matching on all identified risk factors (except contraceptive type). This would provide more evidence of an association of DMPA use with fracture risk, although unidentified confounders could not be excluded as a cause, since the study was not randomized.

We used a retrospective (time-varying) cohort study design because 1) the outcome, non-traumatic fracture, is not rare; 2) it allowed us to assess the incidence of fractures in the study population; 3) there are several potential confounders (which we control for using multivariable analysis) and 4) we were able to directly model contraceptive use as it changed over time by modeling with time-dependent covariates. Typically, the role of matching is not to increase validity of a study, but rather to increase the efficiency of a study by minimizing the number of subjects you need to collect data from. In this study we capitalized on our access to clinical data on the large sample using the EMR. Using a case-control design and matching on known risk factors like alcohol abuse, corticosteroid use, or epilepsy would diminish statistical power by using a smaller group of controls, and not all cases would be guaranteed to have a control that matched on all identified risk factors. We do not think we would increase the validity of our study and we do not have the resources to conduct a what would be a large second analysis of our data using a weaker study design.

ASSOCIATE EDITOR - GYN

Please start the Abstract Conclusion with a more dynamic, meaningful opening statement

The first sentence of the Abstract conclusion has been revised. We have also revised the Precis to correspond with the last sentence of the conclusion of the abstract, which provides a better overall summary.

EDITORIAL OFFICE COMMENTS:

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

We select #1. 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.

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

3. 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.

See Response to Comment#2, Reviewer #1 – Data from administrative and clinical databases at KPNC (the KP HealthConnect Electronic Health Record) are "extracted" directly using SAS programming. Also we discussed validation of the data in the text of the manuscript (line 148-151 of the original submission).

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.

The STROBE checklist has been revised to include the page numbers where each item appears in the REVISED manuscript (clean version.

5. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions. Please access the obstetric and gynecology data definitions at https://www.acog.org/About-ACOG/ACOG-Departments/Patient-Safety-and-Quality-Improvement/reVITALize. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

The manuscript conforms to use of reVITALize definitions.

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.

The REVISED manuscript adheres to the length restrictions; word counts are provided.

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).**

Financial support and contributors (who have provided written approval) have been acknowledged.

8. Provide a précis on the second page, for use in the Table of Contents. The précis is a single sentence of no more than 25 words that states the conclusion(s) of the report (ie, the bottom line). The précis should be similar to the abstract's conclusion. Do not use commercial names, abbreviations, or acronyms in the précis. Please avoid phrases like "This paper presents" or "This case presents."

A 25-word Précis is provided

9. The most common deficiency in revised manuscripts involves the abstract. Be sure there are no inconsistencies between the Abstract and the manuscript, and that the Abstract has a clear conclusion statement based on the results found in the paper. Make sure that the abstract does not contain information that does not appear in the body text. If you submit a revision, please check the abstract carefully.

In addition, the abstract length should follow journal guidelines. The word limits for different article types are as follows: Original Research articles, 300 words. Please provide a word count.

Word counts adhere to guidelines and are provided

10. Only standard abbreviations and acronyms are allowed. A selected list is available online at http://edmgr.ovid.com/ong/accounts/abbreviations.pdf. Abbreviations and acronyms cannot be used in the title or précis. Abbreviations and acronyms must be spelled out the first time they are used in the abstract and again in the body of the manuscript.

Only standard abbreviations are used

11. The journal does not use the virgule symbol (/) in sentences with words. Please rephrase your text to avoid using "and/or," or similar constructions throughout the text. You may retain this symbol if you are using it to express data or a measurement.
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12. We discourage claims of first reports since they are often difficult to prove. How do you know this is the first report? If this is based on a systematic search of the literature, that search should be described in the text (search engine, search terms, date range of search, and languages encompassed by the search). If on the other hand, it is not based on a systematic search but only on your level of awareness, it is not a claim we permit.
We have removed the reference to "first U.S. study" in the discussion.

13. Please review the journal's Table Checklist to make sure that your tables conform to journal style. The Table Checklist is available online here:
http://edmgr.ovid.com/ong/accounts/table_checklist.pdf.
Tables conform

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