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: Feb 26, 2020
To: "John S Barbieri" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-20-153

RE: Manuscript Number ONG-20-153

Influence of contraception class on incidence and severity of acne vulgaris

Dear Dr. Barbieri:

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 Mar 18, 2020, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1:

1.The large subject number of 336,738 patients is impressive and make the results reliable. As you concluded "However, absolute differences between forms of contraception were small." Your study clarified assumptions that are frequently made by prescribers.

2. Your explanation of possible confounding factors is thorough.

While it is possible that these contraception methods may be protective against acne, it is important to consider the possibility of unmeasured confounding. Notably, women who receive the etonogestrel implant and DMPA injections are substantially less likely to have a history of acne
- We therefore urge caution in interpretation of these results because if an unmeasured confounder, such as acne that is not coded, was also associated with decreased risk of subsequent acne codes detected in our study, these findings could be biased.

3. The discussion of a possible explanation of previous findings that COC improve acne is discussed well.
- Prior research has shown that COCs can reduce acne, and this study highlights that COCs are associated with a beneficial effect with respect to acne compared to other options and that the loss of a beneficial effect from COCs when switching to another method may partially explain why other contraception options have traditionally been felt to worsen acne. However, absolute differences between forms of contraception were small.

4. This issue is relevant to patients of dermatologists, gynecologists and primary care providers, as they manage an individual patient's contraception plans and their acne incidence, both very important to the patient.

Reviewer #2: The manuscript by Barbieri and colleagues evaluates the incidence and severity of acne vulgaris by contraceptive class. The investigators performed a large database analysis and concluded that the copper IUD and contraceptive implant has a modest association with acne when compared to a referent group of OCP users.

I have no major concerns with the methodology or the research question. My concern is that this is not new information. As the authors have pointed out in their Introduction: "Several placebo-controlled trials have demonstrated that combined

oral contraceptives (COCs) are an effective treatment for acne and patients with acne are frequently prescribed COCs, with three COC products FDA approved for acne."

Thus, when one compares other methods to OCP users, it is not surprising that we see some increased risk. I was actually surprised that the increased risk is no minimal. One could argue that such a modest association could easily be due to residual confounding.

Thus, my conclusion is that this report offers little new information.

Reviewer #3:

Overall Comments: The authors present results from a retrospective cohort study using a de-identified database evaluating the impact of different contraceptive methods on the incidence and severity of acne vulgaris in the first year following initiation of contraception among women who were new contraceptive users and among women switching contraception methods aged 12-40. Contraception methods addressed include combined oral contraception, progestin-only OCPs, DMPA injection, etonogestrel implant, copper IUD and levonorgestral IUS. Oral contraception was noted to have a protective effect with respect to incident acne and treatment escalation in women with baseline acne. This would make sense as estrogen containing OCPs promotes sex hormone binding globulin and inhibit alpha reductase, both resulting in reduction of circulating androgens which can promote acne. However, absolute risk of acne overall was noted to be very small as were the differences of effects among contraceptive types.

Specific Comments:

1. Abstract: Would include in the Results those contraceptive methods associated with decreased risk of incident acne.

2. Introduction: Please provide hypothesis.

3. Materials and Methods: Well described

4. Results: OK. Tables helpful

5. Discussion: Some perspective regarding how this data should be used in clinical practice would be of interest to readers.

STATISTICAL EDITOR COMMENTS:

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

Table 1: Need to format the entries for history PCOS and for incident acne as n(%), not just as %. Need units for age.

Table 2: Need to clarify whether these are unadjusted or adjusted HRs. Need units for age. There are multiple comparisons in this table, with no adjustment for multiple hypothesis testing. Should show the baseline characteristics of Table 1 for the subsets (incident acne and treatment escalation groups)

Should include in sensitivity analysis a separate analysis after excluding all cases of PCOS.

Table 4: Need units for age.

General: Need to include more exposition of the absolute change in % of patients with acne, rather than just analysis based on hazards or on odds., since most women did not experience incident acne and most with pre-existing acne did not experience escalation.

EDITOR'S COMMENTS:

1. We no longer require that authors adhere to the Green Journal format with the first submission of their papers. However, any revisions must do so. I strongly encourage you to read the instructions for authors (the general bits as well

as those specific to the feature-type you are submitting). The instructions provide guidance regarding formatting, word and reference limits, authorship issues, and other things. Adherence to these requirements with your revision will avoid delays during the revision process, as well as avoid re-revisions on your part in order to comply with the formatting.

2. Line 41: The objective of the abstract should be a simple “To” statement without background 1:

3 Line 46: please characterize the data base—only data from private insurers?

4. Line 48: Where ever in your paper that you describe the ages, please add units.

5. Line 49: Please avoid causal language throughout your manuscript. Your study can identify and quantify associations, but not causation. Language should be changed in the precis, abstract, and manuscript, if causal language is used in those sites. It is an idiosyncratic fact that at the Journal we tend to avoid the use of the word impact to imply the result of a change, preferring to limit "impact" to mean a physical blow. (please change this throughout your paper—for instance, line 65, 80, etc)

6. Line 61. Please note that effect sizes (RR, OR) within the zone of potential bias should be noted as weak. Those effect sizes in the zone of potential interest should be emphasized. (Ref: False alarms and pseudo-epidemics. The limitations of observational epidemiology. Grimes DA, Schulz KF. Ob Gyn 2012;120:920-7)It would be appropriate to say something like “…appear to have a modest (or small) protective effect….” And then you could delete the sentence starting on line 62.

7. Line 64: As one reviewer noted, it is generally known that combined oral contraceptives are protective. Perhaps what is less well known is that progestogen only methods, including LARC methods, may be associated with increased risks. You may want to develop that idea a bit more, if true, in your introduction.

8. Line 71. Are all combined oral contraceptive pills protective?

9. Line 78: Rather than “ a couple of” please replace with “Two”

10. Line 96. What is an “annual covered life” ?

11. Line 142: In your discussion, please make sure you make some comment about the accuracy of coding for acne, particularly by non-dermatologists or pediatricians.

12. Line 159: It seems likely that dermatologists would be more comfortable prescribing COC’s but not the use of LARC. And gynecologists more likely to prescribe LARC or DMPA and less likely to code for acne. This seems like a big issue for your paper.

13. Line 164: Please state why your IRB deemed this exempt.

14. Please consider adding a comparison group of women who did NOT receive prescriptions for contraceptives to your study. The Editors feel this would be an important addition to your study.

15. Line 168: P Values vs Effect Size and Confidence Intervals
- While P values are a central part of inference testing in statistics, when cited alone, often the strength of the conclusion can be misunderstood. Whenever possible, the preferred citation should be in terms of an effect size, such as odds ratio or relative risk or the mean difference of a variable between two groups, expressed with appropriate confidence intervals. When such syntax is used, the P value has only secondary importance and often can be omitted or noted as footnotes in a Table format. Putting the results in the form of an effect size makes the result of the statistical test more clinically relevant and gives better context than citing P values alone.
This is true for the abstract as well as the manuscript, tables and figures.

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

We ask that you provide crude OR’s followed by adjusted OR’s for all relevant variables.

16. Line 213: Thank you very much for NOT overstating your results.

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. Our journal requires that all evidence-based research submissions be accompanied by a transparency declaration statement from the manuscript's lead author. The statement is as follows: "The lead author* affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained." *The manuscript's guarantor.

If you are the lead author, please include this statement in your cover letter. If the lead author is a different person, please ask him/her to submit the signed transparency declaration to you. This document may be uploaded with your submission in Editorial Manager.

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. 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.

5. 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.

6. 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).

7. Provide a short title of no more than 45 characters, including spaces, for use as a running foot.

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. 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.

14. 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 Mar 18, 2020, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Nancy C. Chescheir, MD
Editor-in-Chief

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

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Dear Dr. Chescheir,

Please find our revised manuscript entitled “Influence of contraception class on incidence and severity of acne vulgaris” (ONG-20-153) attached. The manuscript has been revised in response to the reviewers' critiques. We are grateful to the editor and reviewers for their thoughtful suggestions and comments, which have significantly improved the manuscript. Below we have listed the changes made in response to the reviewers’ suggestions. These changes have been incorporated into a revised manuscript and are highlighted with track changes.

The lead author,* John Barbieri, affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained. *The manuscript's guarantor.

Reviewer’s Comments

Reviewer 1:

1.The large subject number of 336,738 patients is impressive and make the results reliable. As you concluded "However, absolute differences between forms of contraception were small." Your study clarified assumptions that are frequently made by prescribers.

2. Your explanation of possible confounding factors is thorough.

While it is possible that these contraception methods may be protective against acne, it is important to consider the possibility of unmeasured confounding. Notably, women who receive the etonogestrel implant and DMPA injections are substantially less likely to have a history of acne

- We therefore urge caution in interpretation of these results because if an unmeasured confounder, such as acne that is not coded, was also associated with decreased risk of subsequent acne codes detected in our study, these findings could be biased.

3. The discussion of a possible explanation of previous findings that COC improve acne is discussed well.

- Prior research has shown that COCs can reduce acne, and this study highlights that COCs are associated with a beneficial effect with respect to acne compared to other options and that the loss of a beneficial effect from COCs when switching to another method may partially explain why other contraception options have traditionally been felt to worsen acne. However, absolute differences between forms of contraception were small.

4. This issue is relevant to patients of dermatologists, gynecologists and primary care providers, as they manage an individual patient's contraception plans and their acne incidence, both very important to the patient.

Thank you for this positive feedback.

Reviewer 2:
The manuscript by Barbieri and colleagues evaluates the incidence and severity of acne vulgaris by contraceptive class. The investigators performed a large database analysis and concluded that the copper IUD and contraceptive implant has a modest association with acne when compared to a referent group of OCP users.

I have no major concerns with the methodology or the research question. My concern is that this is not new information. As the authors have pointed out in their Introduction: "Several placebo-controlled trials have demonstrated that combined oral contraceptives (COCs) are an effective treatment for acne and patients with acne are frequently prescribed COCs, with three COC products FDA approved for acne."

Thus, when one compares other methods to OCP users, it is not surprising that we see some increased risk. I was actually surprised that the increased risk is no minimal. One could argue that such a modest association could easily be due to residual confounding.

Thus, my conclusion is that this report offers little new information.

Thank you for your review of our article and we appreciate your positive feedback regarding the methodology of our study. Although prior studies have evaluated the impact of contraception methods on acne, these studies have often included only limited comparisons (e.g. combined oral contraceptives versus placebo) or relied on patient report for acne outcomes. Our study builds upon this prior literature by more comprehensively evaluating multiple contraception methods in the same study, which is a strength of this work compared to prior research on this topic. Our study is also unique in that it evaluated the effects of switching from one contraceptive method to another, which has not previously been explored in the published literature. In addition, our study may be more generalizable to a real-world setting compared to prior clinical trial data. We have added some additional rationale for the study in the introduction section.

Reviewer 3:

Overall Comments: The authors present results from a retrospective cohort study using a de-identified database evaluating the impact of different contraceptive methods on the incidence and severity of acne vulgaris in the first year following initiation of contraception among women who were new contraceptive users and among women switching contraception methods aged 12-40. Contraception methods addressed include combined oral contraception, progestin-only OCPs, DMPA injection, etonogestrel implant, copper IUD and levonorgestral IUS. Oral contraception was noted to have a protective effect with respect to incident acne and treatment escalation in women with baseline acne. This would make sense as estrogen containing OCPs promotes sex hormone binding globulin and inhibit alpha reductase, both resulting in reduction of circulating androgens which can promote acne. However, absolute risk of acne overall was noted to be very small as were the differences of effects among contraceptive types.

Specific Comments:

1. Abstract: Would include in the Results those contraceptive methods associated with decreased risk of incident acne.

Thank you for this suggestion. Compared to combined oral contraceptives (the reference group), none of the evaluated contraception methods was consistently associated with decreased risk of incident acne or treatment escalation. As a result, we did not have any results of contraception methods associated with decreased risk of incident acne to include in the abstract.

2. Introduction: Please provide hypothesis.

Thank you for this helpful suggestion. We have included a statement regarding our study hypotheses at the end of the introduction section.

3. Materials and Methods: Well described
4. Results: OK. Tables helpful

Thank you for this positive feedback.

5. Discussion: Some perspective regarding how this data should be used in clinical practice would be of interest to readers.

Thank you for this helpful suggestion. We have added a line to the final paragraph regarding how this data can be applied to clinical practice.

Statistical editor comments:
Table 1: Need to format the entries for history PCOS and for incident acne as n(%), not just as %. Need units for age.

Thank you for this helpful suggestion. We have updated the Table as suggested.

Table 2: Need to clarify whether these are unadjusted or adjusted HRs. Need units for age. There are multiple comparisons in this table, with no adjustment for multiple hypothesis testing. Should show the baseline characteristics of Table 1 for the subsets (incident acne and treatment escalation groups)

Thank you for this important clarification question. These results are adjusted HRs, which is indicated by the "adj" at the top of each column. We have added a footnote to clarify this detail in the revised Tables. There is only one comparison, which is the impact of the categorical variable of contraception method with our outcome. The other variables are all covariates that were included in the models, as described in the methods (the HRs for these covariates are presented for completeness). If it would be clearer to present only the data on the association of contraception method with acne, we can remove the other rows from the Table.

Should include in sensitivity analysis a separate analysis after excluding all cases of PCOS.

Thank you for this useful suggestion. We have performed a sensitivity analysis (below), which did not identify any notable differences from our primary analysis in Table 2. As a result, we have not included the detailed results of this sensitivity analysis in the article, but we have added a description of this sensitivity analysis to the text of the results section.

Table 2 Sensitivity Analysis Excluding All Women with a History of PCOS

	Incident Acne	**Treatment Escalation**
	HR (95% CI), adj	**HR (95% CI), adj**
Contraception Class		
Combined oral contraceptive	[Reference]	[Reference]
Progestin-only oral contraceptive	1.13 (0.95 to 1.34)	1.34 (0.79 to 2.28)
Copper Intrauterine Device	1.14 (1.00 to 1.29)	1.47 (1.02 to 2.10)
Levonorgestrel Intrauterine Device	1.09 (1.03 to 1.17)	1.32 (1.08 to 1.62)
Etonogestrel Implant	0.83 (0.73 to 0.95)	0.66 (0.41 to 1.05)
DMPA Injection	0.71 (0.59 to 0.84)	0.85 (0.48 to 1.50)
History of polycystic ovarian syndrome		
Calendar year contraception was started	1.04 (1.03 to 1.04)	0.99 (0.97 to 1.01)
Non-acne visits prior to index date, sqrt	0.88 (0.86 to 0.89)	0.98 (0.95 to 1.02)
Non-acne visits after index date, sqrt	1.24 (1.23 to 1.26)	1.09 (1.05 to 1.13)
Age		

<20, years-old	[Reference]	[Reference]
20-24, years-old	0.82 (0.78 to 0.87)	0.84 (0.74 to 0.94)
25-29, years-old	0.82 (0.78 to 0.86)	1.04 (0.89 to 1.21)
30-34, years-old	0.62 (0.59 to 0.66)	0.76 (0.63 to 0.92)
35-40, years-old	0.47 (0.45 to 0.50)	0.67 (0.55 to 0.83)

Table 4 Sensitivity Analysis Excluding All Women with a History of PCOS

	Incident Acne
	HR (95% CI), adj
Contraception Class	
Combined oral contraceptive	[Reference]
Progesterone only oral contraceptive	1.75 (1.27 to 2.42)
Copper Intrauterine Device	1.71 (1.27 to 2.31)
Levonorgestrel Intrauterine Device	1.96 (1.71 to 2.25)
Etonogestrel Implant	1.42 (1.05 to 1.91)
DMPA Injection	0.64 (0.30 to 1.34)
None	1.04 (0.95 to 1.13)
History of polycystic ovarian syndrome	
Calendar year contraception was started	1.02 (1.01 to 1.04)
Non-acne visits prior to index date, sqrt	1.00 (0.98 to 1.03)
Non-acne visits after index date, sqrt	1.12 (1.09 to 1.14)
Age	
<20 years-old	[Reference]
20-24 years-old	0.97 (0.88 to 1.08)
25-29 years-old	1.04 (0.94 to 1.15)
30-34 years-old	0.94 (0.85 to 1.04)
35-40 years-old	0.71 (0.64 to 0.79)

Table 4: Need units for age.

Thank you for this helpful suggestion. We have updated the Table as suggested.

General: Need to include more exposition of the absolute change in % of patients with acne, rather than just analysis based on hazards or on odds., since most women did not experience incident acne and most with pre-existing acne did not experience escalation.

Thank you for this helpful suggestion. We agree that absolute risk is important, which is why we have included these data in Table 1. We added more explicit reference to this in the results and discussion.

Editor's comments:

1. We no longer require that authors adhere to the Green Journal format with the first submission of their papers. However, any revisions must do so. I strongly encourage you to read the instructions for authors (the general bits as well as those specific to the feature-type you are submitting). The instructions provide guidance regarding formatting, word and reference limits, authorship issues, and other things. Adherence to these requirements with your revision will avoid delays during the revision process, as well as avoid re-revisions on your part in order to comply with the formatting.

Thank you for this helpful suggestion. We have updated the article in these revisions to align with the formatting requirements and have carefully reviewed the Instructions for Authors (http://edmgr.ovid.com/ong/accounts/authors.pdf).

2. Line 41: The objective of the abstract should be a simple "To" statement without background 1:

We have adjusted the Objective section of the abstract as suggested.

3 Line 46: please characterize the data base—only data from private insurers?

We have clarified that it is a commercial claims database in the abstract, which is also described in the "Data source" section of the Methods.

4. Line 48: Where ever in your paper that you describe the ages, please add units.

We have added units when we describe ages throughout the article.

5. Line 49: Please avoid causal language throughout your manuscript. Your study can identify and quantify associations, but not causation. Language should be changed in the precis, abstract, and manuscript, if causal language is used in those sites. It is an idiosyncratic fact that at the Journal we tend to avoid the use of the word impact to imply the result of a change, preferring to limit "impact" to mean a physical blow. (please change this throughout your paper—for instance, line 65, 80, etc)

Thank you for this helpful comment. We have adjusted the language throughout the article as suggested.

6. Line 61. Please note that effect sizes (RR, OR) within the zone of potential bias should be noted as weak. Those effect sizes in the zone of potential interest should be emphasized. (Ref: False alarms and pseudo-epidemics. The limitations of observational epidemiology. Grimes DA,

Schulz KF. Ob Gyn 2012;120:920-7)It would be appropriate to say something like "…appear to have a modest (or small) protective effect…." And then you could delete the sentence starting on line 62.

Thank you for this helpful suggestion. We have adjusted the text of the sentence as suggested.

7. Line 64: As one reviewer noted, it is generally known that combined oral contraceptives are protective. Perhaps what is less well known is that progestogen only methods, including LARC methods, may be associated with increased risks. You may want to develop that idea a bit more, if true, in your introduction.

Thank you for this useful suggestion. We have updated the introduction to develop the concept that there is a need for additional data on the effects of progesterone only methods and LARC methods on acne incidence and severity.

8. Line 71. Are all combined oral contraceptive pills protective?

Thank you for this helpful question. The cited Cochrane systematic review found that each of the six combined oral contraceptives evaluated in placebo-controlled trials were effective for acne (PMID: 22786490). There were no significant differences noted between different combined oral contraceptive preparations suggesting that it is likely that all combined oral contraceptive pills may be helpful for acne.

9. Line 78: Rather than " a couple of" please replace with "Two"

We have adjusted the text as suggested.

10. Line 96. What is an "annual covered life" ?

Thank you for this clarification question. It is a measure of the size of the database, similar to a "person-year" in an epidemiological study. An annual covered life is a patient who was covered by the commercial insurance plans included in the database for that year. It reflects that for each year of data, there are approximately 12-14 million individuals who could have a claim in the dataset (although they may have no claims if they did not interact with the healthcare system). We have simplified the text to describe the database as including "de-identified commercial claims data for approximately 12-14 million individuals annually."

11. Line 142: In your discussion, please make sure you make some comment about the accuracy of coding for acne, particularly by non-dermatologists or pediatricians.

Thank you for these helpful comments. While ICD codes have been validated for acne, these studies were performed among a dermatology population, and the accuracy of these codes has not been extensively evaluated in a non-dermatology population (e.g. pediatricians, primary care providers); we added a discussion of this issue and a citation to the limitations section of the manuscript.

12. Line 159: It seems likely that dermatologists would be more comfortable prescribing COC's but not the use of LARC. And gynecologists more likely to prescribe LARC or DMPA and less likely to code for acne. This seems like a big issue for your paper.

We agree that dermatologists may be more likely to prescribe COCs and code acne. However, dermatologists are probably unlikely to prescribe COCs prior to coding for acne, making this less of an issue for our primary analysis of incident acne. Further, if dermatologists were to be more likely to prescribe combined oral contraceptives and subsequently more likely to code for acne in patients with clinical acne, this would bias our results towards the null (i.e. make combined oral contraceptives appear less strongly associated with a beneficial effect compared to other contraceptives). We have added a discussion of this issue to the limitations section of the article.

13. Line 164: Please state why your IRB deemed this exempt.

We have clarified that the study was exempt since it involved the use of de-identified data.

14. Please consider adding a comparison group of women who did NOT receive prescriptions for contraceptives to your study. The Editors feel this would be an important addition to your study.

We agree that this could be an important addition. In fact, when we were in the process of developing the protocol for this project, we extensively discussed whether to include a comparison group who did not receive prescriptions for contraceptives as part of our primary analysis. However, since the probability of receiving a code for acne is likely associated with interaction with the healthcare system, it is difficult to define an appropriate comparison group of patients who did not receive prescriptions for contraceptives without potentially introducing additional sources of bias. For example, we considered using women who received cervical cancer screening as a comparator group, but were concerned about temporal changes in US guidelines for screening and differences by age group. Given the challenges of defining an appropriate comparator group and the high risk of potential bias, we decided that it would not be optimal to include a comparator group of those who do not have any prescriptions for contraceptives as part of the primary analysis.

15. Line 168: P Values vs Effect Size and Confidence Intervals
- While P values are a central part of inference testing in statistics, when cited alone, often the strength of the conclusion can be misunderstood. Whenever possible, the preferred citation should be in terms of an effect size, such as odds ratio or relative risk or the mean difference of a variable between two groups, expressed with appropriate confidence intervals. When such syntax is used, the P value has only secondary importance and often can be omitted or noted as footnotes in a Table format. Putting the results in the form of an effect size makes the result of the statistical test more clinically relevant and gives better context than citing P values alone. This is true for the abstract as well as the manuscript, tables and figures.

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

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

Thank you for this helpful feedback. Throughout the article we present effect estimates and 95% confidence intervals, rather than p-values, and we agree with the rationale described above. In the revisions, we have included crude HRs in the Tables, although we urge caution with their interpretation given the important influence of covariates such as age on our outcomes of interest.

16. Line 213: Thank you very much for NOT overstating your results.

Thank you for this positive feedback.

Thank you for your continued consideration of this work. Please do not hesitate to contact us with any questions or clarifications. We look forward to hearing from you.

Sincerely,

John Barbieri MD, MBA