

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)*
- Email correspondence between the editorial office and the authors*

**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: Jan 04, 2019
To: "Yolanda Munoz Balbontin" [REDACTED]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-18-2071

RE: Manuscript Number ONG-18-2071

Herbal medicinal products use during pregnancy and the postnatal period: a systematic review of reported safety issues

Dear Dr. Munoz Balbontin:

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 Jan 25, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: In this systematic review Balbontin and colleagues examine the existing body of published evidence on the use of herbal products in obstetrics. The manuscript is very well written, the methodology clearly defined, and despite the large amount of material, the findings are presented in an organized manner for the reader. This topic is timely and of interest to the readers of the journal as there is a significant movement nationwide toward the use of herbal supplements in lieu of prescription pharmacotherapy (i.e. Cinnamon extract and chromium picolinate for GDM, Primrose oil for induction), and we are often asked to provide an opinion on the safety of various agents.

The abstract, introduction, methods, results, and conclusions were spot on. The PRISMA guidelines were followed. My only suggestion is to add a sentence to the limitations/weakness section of the discussion to the effect that not all herbal agents were included. As I mentioned above, Cinnamon and Primrose oil are commonly used in the States and I didn't see a mention of the them in the report even though there are 10-20 published reports for each in the database I quickly searched during my review of this manuscript.

Reviewer #2: The manuscript entitled "Herbal medicinal products use during pregnancy and the postnatal period: a systematic review of reported safety issues" is a novel and useful study shows the impacts of some herbal medicinal products on the pregnancy and postnatal period. Also, although the study is comprehensive, there is no discussion about animal studies. However, there are several things that should be written or added to the article;

1. One and/or two figures that show the shape of the plants or the active components of them should be added to the study.
2. One of the purposes of the review articles is a help to readers to find a new idea to do a different work and/or complete the rudimentary studies. However, in this study, there was no discussion for the molecular mechanisms to show how for example; the herb-drug interaction occurs.
3. It is better to write general information about the possible mechanisms of the active components on pregnancy outcomes in the discussion section, in 200-500 words.

Reviewer #3: Balbontin and colleagues present a systematic review of herbal medicinal products used during pregnancy and post-partum period. The manuscript is well-written and explores an understudied area of perinatal research. The authors provide a clear literature search schema and manuscript inclusion/exclusion criterion. A search of abstracts does not appear to have been included as part of the review. The literature for multiple herbal agents, however, was limited to only 74 papers spanning 47 herbal agents with diverse study quality and outcomes assessed. This limited literature limits definitive conclusions as noted by the authors. A point-by-point critique of the paper follows:

- 1) The search strategy used for the study appears to have focused on published manuscripts. A total of 74 manuscripts were identified but only 29 of which were intervention studies. 19 papers included were case reports. There is risk of over estimating adverse events with inclusion of case reports (which would have a higher likelihood of publication) and under-estimating adverse outcomes (negative studies are not likely to be published beyond manuscript form. How was publication bias assessed? Was there any attempt to search abstracts of proceedings from major scientific meetings for additional citations?
- 2) The outcomes assessed in the manuscript were diverse ranging from preterm birth, cesarean delivery, maternal morbidity, and neonatal morbidity and mortality. These outcomes are rather vague and with multiple other potential modulating factors, clearly defining association with a given herbal agent with an outcome is challenging. No consideration of dose-effect (aside from licorice) is able to be explored. How do the authors see that the findings from this systematic review will be used by clinicians to guide clinical practice and patient counseling?
- 3) The Abstract and Results section of the paper note that the review includes only 2 randomized trials however from Table 1 and 2 it appears that there is at least 23 randomized trials. Why is the statement in the Abstract/Results section of the paper divergent?
- 4) From the Tables, it appears that for most of the randomized trials (presumably the herbal agent was the primary intervention), there were no major adverse perinatal outcomes. As this is the highest quality of evidence and likely at lower risk for bias, why did the authors not restrict their analysis to these type of studies, or at least restrict to randomized trials and cohort studies?
- 5) The Tables are excessive, but necessary to report related to the individual studies. Table 2 column "nature" is vague and should be revised. Perhaps having a column for adverse side effects and a separate column for adverse perinatal outcome would make the table easier to read.
- 6) Table 2: A column for "causality established" is included. How is causality established? Even randomized trials can only establish associations, not causality. How do the authors make this inference? What criterion were used, aside from the primary papers author proclamation, to define "causality established" by the authors of this paper?

Reviewer #4: The authors are to be congratulated for an extensive review of the use of herbal supplements/medications during pregnancy and the postpartum period. I have no specific comments other than that Tables 3 and 4 provide more detailed information than is useful for the audience to which this is addressed. The detailed information on individual herbal treatments is available to any interested reader by searching the extensive reference list of the authors. The more important message of this paper is that there is no information to support the safety of any of these substances in pregnancy.

STATISTICAL EDITOR COMMENTS:

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

Table 2: It is difficult to generalize from the case reports, since there is no estimate of incidence and no control. The studies should include some indication of the size of the series and the number of hypotheses tested. For instance, if ten comparisons were done and one association was found to have an association at the $p < .05$ level, that allows a much weaker conclusion than if only one hypothesis were tested using the same inference threshold. Also, by definition, the number of herbal agents included is broad, so it is difficult to generalize any conclusion.

Fig 3: As implied by these ORs, the wide confidence intervals mean that the numbers of adverse events is small. Almost all of the ORs have lower CI boundaries close to 1.0. Further studies may not replicate a significant finding.

Suggest much of material could be on-line with summary of studies to include sample size, outcome(s) of interest and

brief summary of population studied.

EDITOR COMMENTS:

1. Thank you for your submission to Obstetrics & Gynecology. In addition to the comments from the reviewers above, you are being sent a notated PDF that contains the Editor's specific comments. Please review and consider the comments in this file prior to submitting your revised manuscript.

The notated PDF is uploaded to this submission's record in Editorial Manager. If you cannot locate the file, contact Randi Zung and she will send it by email - rzung@greenjournal.org.

2. 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.

3. 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.

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: Review articles should not exceed 25 typed, double-spaced pages (6,250 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. Titles in Obstetrics & Gynecology are limited to 100 characters (including spaces). Do not structure the title as a declarative statement or a question. Introductory phrases such as "A study of..." or "Comprehensive investigations into..." or "A discussion of..." should be avoided in titles. Abbreviations, jargon, trade names, formulas, and obsolete terminology also should not be used in the title. Titles should include "A Randomized Controlled Trial," "A Meta-Analysis," or "A Systematic Review," as appropriate, in a subtitle. Otherwise, do not specify the type of manuscript in the title.

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: Reviews, 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. Line 440: 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.

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. Figures

Figure 1: Please edit or explain n value for full-text records screened (3,487–3,389=98).

Figure 2 and Figure 3 may be resubmitted with the revision.

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.

15. 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 Jan 25, 2019, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Nancy C. Chescheir, MD
Editor-in-Chief

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

In compliance with data protection regulations, please contact the publication office if you would like to have your personal information removed from the database.

Aberdeen, Scotland, United Kingdom
23rd of January 2019

Dear editor,

The authors wish to thank your team for their comments and suggestions. Please find our answers to these below:

RE: Manuscript Number ONG-18-2071

Herbal medicinal products use during pregnancy and the postnatal period: a systematic review of reported safety issues

Dear Dr. Munoz Balbontin:

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 Jan 25, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1:

In this systematic review Balbontin and colleagues examine the existing body of published evidence on the use of herbal products in obstetrics. The manuscript is very well written, the methodology clearly defined, and despite the large amount of material, the findings are presented in an organized manner for the reader. This topic is timely and of interest to the readers of the journal as there is a significant movement nationwide toward the use of herbal supplements in lieu of prescription pharmacotherapy (i.e. Cinnamon extract and chromium picolinate for GDM, Primrose oil for induction), and we are often asked to provide an opinion on the safety of various agents. The abstract, introduction, methods, results, and conclusions were spot on. The PRISMA guidelines were followed

The authors thank the referee for their very supportive comments

1. My only suggestion is to add a sentence to the limitations/weakness section of the discussion to the effect that not all herbal agents were included.

As suggested the following sentence has now been modified at the end of the “Strengths and Weaknesses of the Review” to clarify: “Due to the large number of herbal medicinal products available worldwide and the lack of standardization in reporting the names of herbal medicinal products, it is possible that relevant literature was omitted and not all herbal medicinal products were reported”.

2. As I mentioned above, Cinnamon and Primrose oil are commonly used in the States and I didn't see a mention of the them in the report even though there are 10-20 published reports for each in the database I quickly searched during my review of this manuscript.

Primrose oil was reported in Tables 2, and 4 included in this manuscript. As for cinnamon, the referee is correct and there are a number of reports in the literature. However these reports did not meet the criteria for inclusion in this systematic review.

This point has been highlighted in the “Strengths and Weaknesses of the Review” section of our review as stated above.

Reviewer #2:

The manuscript entitled "Herbal medicinal products use during pregnancy and the postnatal period: a systematic review of reported safety issues" is a novel and useful study shows the impacts of some herbal medicinal products on the pregnancy and postnatal period. Also, although the study is comprehensive, there is no discussion about animal studies. However, there are several things that should be written or added to the article;

1. One and/or two figures that show the shape of the plants or the active components of them should be added to the study.

This systematic review discusses 47 different herbs and plants and the authors felt adding the shape of the plants together with the active components (where known) would shift the focus of the manuscript and confuse the readers who might expect a botanic/biochemical review of the herbal medicines.

2. One of the purposes of the review articles is a help to readers to find a new idea to do a different work and/or complete the rudimentary studies. However, in this study, there was no discussion for the molecular mechanisms to show how for example; the herb-drug interaction occurs.

The reviewer is correct however the molecular mechanisms of herb-drug interactions are frequently unknown and were not a review objective.

The following sentence has been added to the “Eligibility” subsection of the manuscript to clarify this point: “The shape, active components, and molecular mechanisms of the herbal medicinal products were not a review objective and will not be discussed in this paper.”

3. It is better to write general information about the possible mechanisms of the active components on pregnancy outcomes in the discussion section, in 200-500 words.

This again was not a review objective and the mechanisms underlying actions on pregnancy outcomes are frequently unknown. Therefore, any discussion would be speculative and change the focus of this review.

Reviewer #3:

Balbontin and colleagues present a systematic review of herbal medicinal products used during pregnancy and post-partum period. The manuscript is well-written and explores an understudied area of perinatal research the authors provide a clear literature search schema and manuscript inclusion/exclusion criterion.

The authors would like to thank the referee for these very kind comments

1. The search strategy used for the study appears to have focused on published manuscripts. A total of 74 manuscripts were identified but only 29 of which were intervention studies. 19 papers included were case reports. There is risk of over estimating adverse events with inclusion of case reports (which would have a higher likelihood of publication) and under-estimating adverse outcomes (negative studies are not likely to be published beyond manuscript form. How was publication bias assessed? Was there any attempt to search abstracts of proceedings from major scientific meetings for additional citations?

The referee has identified several of the difficulties of conducting a systematic review of this type. Several previous reviews have excluded case reports hence our decision to include these. Case studies were only included when reported as a full scientific paper. In addition, case reports are also an important source of pharmacovigilance data, many of this result in drug withdrawal from the market.

Publication bias is also a limitation of all systematic reviews but perhaps less so in reviews of adverse events. We chose not to include conference abstracts or grey literature for several reasons including the vast number of conferences at which abstracts describing herbal products could be submitted. Furthermore, the methodology described in abstracts would be insufficient for assessment of quality and results insufficient for data extraction and synthesis.

2. The outcomes assessed in the manuscript were diverse ranging from preterm birth, caesarean delivery, maternal morbidity, and neonatal morbidity and mortality. These outcomes are rather vague and with multiple other potential modulating factors, clearly defining association with a given herbal agent with an outcome is challenging. No consideration of dose-effect (aside from liquorice) is able to be explored.

One of the objectives of this systematic review is to highlight the significant lack of robust scientific evidence obtained from well-designed studies despite the remarkably wide spread use of herbal agents during pregnancy. An awareness and recognition of the paucity of safety and outcome data, which we have highlighted, should help clinicians to appropriately advise their

patients about the use of herbal medicinal products throughout pregnancy until proper evidence is available.

Unfortunately, we could not address dose effects because apart from liquorice these were not reported in the reviewed papers, which highlights a further issue in the published literature.

3. The Abstract and Results section of the paper note that the review includes only 2 randomized trials however from Table 1 and 2 it appears that there is at least 23 randomized trials. Why is the statement in the Abstract/Results section of the paper divergent?

The referee has misunderstood the abstract. There is no mention in the abstract of only two randomized trials being included. The abstract does say that of the 74 included studies only 19 reported adverse events as their primary objective of which only two were randomised clinical trials. The remainder of the 74 studies either included adverse events as a secondary objective or reported them as a side-note.

The abstract has been modified to clarify this.

4. From the Tables, it appears that for most of the randomized trials (presumably the herbal agent was the primary intervention), there were no major adverse perinatal outcomes. As this is the highest quality of evidence and likely at lower risk for bias, why did the authors not restrict their analysis to these types of studies, or at least restrict to randomized trials and cohort studies?

The majority of the reviewed published studies failed to comment on adverse events and only a small number included adverse events as a primary outcome. Therefore, by restricting the review in the way suggested we would have failed to identify relevant adverse events, which were not reported or investigated in the majority of clinical trials and cohort studies. By including case reports we obtained a view of the possible adverse events presenting in the population not included in clinical trials and cohorts.

5. The Tables are excessive, but necessary to report related to the individual studies. Table 2 column "nature" is vague and should be revised. Perhaps having a column for adverse side effects and a separate column for adverse perinatal outcome would make the table easier to read.

The referee is correct and as with all systematic reviews by necessity the tables are excessive. The majority tables will be included as Supplementary Digital Content (SDC) and only a short table reporting relevant herbal medicinal products with reported adverse events will be included.

6. Table 2: A column for "causality established" is included. How is causality established? Even randomized trials can only establish associations, not causality. How do the authors make this inference? What criterion were used, aside from the primary papers author proclamation, to define "causality established" by the authors of this paper?

The referee is correct and as suggested the term causality has been removed from the manuscript and tables.

Reviewer #4:

The authors are to be congratulated for an extensive review of the use of herbal supplements/medications during pregnancy and the postpartum period. I have no specific comments other than that Tables 3 and 4 provide more detailed information than is useful for the audience to which this is addressed. The detailed information on individual herbal treatments is available to any interested reader by searching the extensive reference list of the authors. The more important message of this paper is that there is no information to support the safety of any of these substances in pregnancy.

The authors are in full agreement with the referee and thank them for their supportive comments. As suggested the tables have now been moved to digital content and a simplified reader friendly table is included in the main paper.

STATISTICAL EDITOR COMMENTS:

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

1. Table 2: It is difficult to generalize from the case reports, since there is no estimate of incidence and no control. The studies should include some indication of the size of the series and the number of hypotheses tested. For instance, if ten comparisons were done and one association was found to have an association at the $p < .05$ level, that allows a much weaker conclusion than if only one hypothesis were tested using the same inference threshold. Also, by definition, the number of herbal agents included is broad, so it is difficult to generalize any conclusion.

The authors agree with the statistician's comments. Great effort went into making the conclusions as clear as possible.

2. Fig 3: As implied by these ORs, the wide confidence intervals mean that the numbers of adverse events is small. Almost all of the ORs have lower CI boundaries close to 1.0. Further studies may not replicate a significant finding.

Again, the authors agree with the statistician's comments. The forest plot was included only to report the data in visual form. Considering the very wide confidence intervals, the plot was formatted with the midpoint (1) to the left of the chart for aesthetic reasons.

3. Suggest much of material could be on-line with summary of studies to include sample size, outcome(s) of interest and brief summary of population studied.

The authors agree with the statistician. The tables have been included as supplementary digital content.

EDITOR COMMENTS:

1. Thank you for your submission to Obstetrics & Gynecology. In addition to the comments from the reviewers above, you are being sent a notated PDF that contains the Editor's specific comments. Please review and consider the comments in this file prior to submitting your revised manuscript.

The notated PDF is uploaded to this submission's record in Editorial Manager. If you cannot locate the file, contact Randi Zung and she will send it by email - rzung@greenjournal.org.

The authors thank the editor for her comments and have accessed the notated PDF document and worked on the comments.

2. 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.

3. 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 co-authors 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.

The authors will complete the eCTA as requested.

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.

The definitions have been reviewed and we do not find it problematic to follow them.

5. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Review articles should not exceed 25 typed, double-spaced pages (6,250 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 manuscript is 22 pages and 4,200 words, excluding references and supplementary content (which will be made available online).

6. Titles in Obstetrics & Gynecology are limited to 100 characters (including spaces). Do not structure the title as a declarative statement or a question. Introductory phrases such as "A study of..." or "Comprehensive investigations into..." or "A discussion of..." should be avoided in titles. Abbreviations, jargon, trade names, formulas, and obsolete terminology also should not be used in the title. Titles should include "A Randomized Controlled Trial," "A Meta-Analysis," or "A Systematic Review," as appropriate, in a subtitle. Otherwise, do not specify the type of manuscript in the title.

Our title is 17 words long and mentions the article is a systematic review.

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).

All funding parties were acknowledged in said section. Persons who contributed to the work of the manuscript qualified as authors and were listed as such.

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: Reviews, 300 words. Please provide a word count.

The abstract has been modified to clarify referee comments. The word count is 310 words.

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.

All abbreviations have been worded out and only internationally official abbreviations have been included.

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.

The virgule symbol has been removed from the manuscript.

11. Line 440: 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.

This primacy claim has been removed.

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.

The authors have reviewed the journal's checklist. The tables have been modified to fit the latter and as suggested by the referees and statistician.

13. Figures

Figure 1: Please edit or explain n value for full-text records screened (3,487–3,389=98).

By "Full-text records screened", the authors mean that 93 articles were read in full to be considered for inclusion or exclusion in the review.

The figure has been modified as suggested: "Records read in full to consider for inclusion" has substituted "Full-text records screened".

Figure 2 and Figure 3 may be resubmitted with the revision.

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/ifaauth.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.

The authors are aware of this. Thank you.

15. 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 Jan 25, 2019, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Nancy C. Chescheir, MD
Editor-in-Chief

2017 IMPACT FACTOR: 4.982

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

From: [REDACTED]
To: [Randi Zung](mailto:Randi.Zung)
Subject: Re: Your Revised Manuscript 18-2275R1
Date: Thursday, January 31, 2019 3:06:10 PM

Thank you for improving the sentence. Much better!

Erinn

From: Randi Zung <RZung@greenjournal.org>
Date: Thursday, January 31, 2019 at 3:04 PM
To: "Myers, Erinn M" [REDACTED]
Subject: RE: Your Revised Manuscript 18-2275R1

WARNING: This email originated from outside of Atrium Health (RZung@greenjournal.org).

Do not click links or open attachments unless you recognize the sender and are expecting the message.

Dear Dr. Myers:

We are going to reword your Acknowledgement statement to say, "The authors thank the Carolinas Simulation Center for the material support and teammate time." This will bring it in line with journal style.

Thanks,
Randi

From: Myers, Erinn M [REDACTED]
Sent: Thursday, January 31, 2019 2:31 PM
To: Randi Zung <RZung@greenjournal.org>
Subject: Re: Your Revised Manuscript 18-2275R1

Dear Randi Zung,

Thank you for your email. I will reach out to the co-authors about the Copyright Transfer Agreement.

In the mean time here are the revisions and we approve all edits.

Thank you

Erinn M. Myers, MD FACOG FPMRS FACS

[REDACTED]




Atrium Health

Carolinas HealthCare System is Atrium Health

From: Randi Zung <RZung@greenjournal.org>

Date: Thursday, January 31, 2019 at 11:15 AM

To: "Myers, Erinn M" 

Subject: Your Revised Manuscript 18-2275R1

WARNING: This email originated from outside of Atrium Health (RZung@greenjournal.org).

Do not click links or open attachments unless you recognize the sender and are expecting the message.

Dear Dr. Myers:

Your revised manuscript is being reviewed by the Editors. Before a final decision can be made, we need you to address the following queries. Please make the requested changes to the latest version of your manuscript that is attached to this email. **Please track your changes and leave the ones made by the Editorial Office.** Please also note your responses to the author queries in your email message back to me.

1. General: The Manuscript Editor and Dr. Chescheir have made edits to the manuscript using track changes. Please review them to make sure they are correct.
2. Electronic Copyright Transfer Agreement: All co-authors will need to complete our electronic Copyright Transfer Agreement, which was sent to them through Editorial Manager (EM@greenjournal.org). Our records show that none of your co-authors have completed this form in full yet.
3. Line 32: Why was this information included? Not sure where this should go...

To facilitate the review process, we would appreciate receiving a response by February 4.

Best,
Randi Zung

--

Randi Zung (Ms.)

Editorial Administrator | *Obstetrics & Gynecology*
American College of Obstetricians and Gynecologists
409 12th Street, SW
Washington, DC 20024-2188
T: 202-314-2341 | F: 202-479-0830

This electronic message may contain information that is confidential and/or legally privileged. It is intended only for the use of the individual(s) and entity named as recipients in the message. If you are not an intended recipient of this message, please notify the sender immediately and delete the material from any computer. Do not deliver, distribute or copy this message, and do not disclose its contents or take any action in reliance on the information it contains. Thank you.

This electronic message may contain information that is confidential and/or legally privileged. It is intended only for the use of the individual(s) and entity named as recipients in the message. If you are not an intended recipient of this message, please notify the sender immediately and delete the material from any computer. Do not deliver, distribute or copy this message, and do not disclose its contents or take any action in reliance on the information it contains. Thank you.

From: [REDACTED]
To: [Stephanie Casway](#)
Subject: Re: O&G Figure Revision: 18-2071
Date: Wednesday, January 30, 2019 9:23:41 AM

Hello,

Yes, that's correct.

Best wishes,

Yolanda

Get [Outlook for Android](#)

From: Stephanie Casway <SCasway@greenjournal.org>
Sent: Wednesday, January 30, 2019 1:53:19 PM
To: Munoz Balbontin, Yolanda
Subject: RE: O&G Figure Revision: 18-2071

CAUTION: This email contains web links. Do NOT click on these links unless you recognise the sender and know the content is safe.

Hi Yolanda,

Would it be correct to update the records excluded to 3,394? Thanks so much!

From: Munoz Balbontin, Yolanda [REDACTED]
Sent: Wednesday, January 30, 2019 8:52 AM
To: Stephanie Casway <SCasway@greenjournal.org>
Subject: Re: O&G Figure Revision: 18-2071

Hello,

You are correct Stephanie. Sorry for that miscalculation.

Thanks again!

Yolanda

Get [Outlook for Android](#)

From: Stephanie Casway <SCasway@greenjournal.org>
Sent: Wednesday, January 30, 2019 1:42:15 PM
To: Munoz Balbontin, Yolanda
Subject: RE: O&G Figure Revision: 18-2071

CAUTION: This email contains inline pictures or attached content. Do NOT open attachments unless you recognise the sender and know the content is safe.

Hi Yolanda,

Thank you so much for your review. I have updated Figure 2 and 3 with your edits (see attached). I am a little confused about the n values in Figure 1 still. Does the n value for records excluded (n=3,389) need to be updated? When I remove those records from those screened, I get 98 rather than 93.

From: Munoz Balbontin, Yolanda [REDACTED]
Sent: Wednesday, January 30, 2019 5:25 AM
To: Stephanie Casway <SCasway@greenjournal.org>
Subject: Re: O&G Figure Revision: 18-2071

Hello Stephanie,

Many thanks for this revision. The legends are correct and to answer your queries:

AQ1: The n value at the top of Figure 1 is correct.

AQ2: The y-axis labels you included are correct.

AQ3: For the second graph of Figure 2 from left to right; Chuang 2006 (91), Chuang 2006 (92), Strandberg 2002, Strandberg 2001, Heitmann 2016, Heitmann 2013 (72), Heitmann 2013 (74), Raikkonen 2009, Raikkonen 2017. Since a few of the studies were reported the same year I included the reference number that corresponds to each to tell them apart.

AQ4: The label is incorrect, it should read **OR (95% CI)**

AQ5: Most of the reference numbers are incorrect, I overlooked modifying these when revising the manuscript for the reviewers and editor. Apologies. The correct numbers are: Senna 90, Huang Lian 91, An-Tai-Yin 91, Almond oil 94, Raspberry leaf 34, Licorice 78, 79, 97, 98, Mwanaphepo 100.

Please let me know if anything else needs clarification.

All the best,

Yolanda

From: Stephanie Casway <SCasway@greenjournal.org>

Sent: 29 January 2019 18:07:13

To: Munoz Balbontin, Yolanda

Subject: O&G Figure Revision: 18-2071

CAUTION: This email contains inline pictures or attached content. Do NOT open attachments unless you recognise the sender and know the content is safe.

Good Afternoon Dr. Balbontin,

Your figures and legend have been edited, and PDFs of the figures and legend are attached for your review. Please review the figures CAREFULLY for any mistakes. In addition, please see our queries below.

AQ1: Please review the n values at the top of Figure 1 (3487-3389=98).

AQ2: We have added y-axis labels in Figure 2. Please let me know if these are incorrect.

AQ3: Please provide year of publication for studies that appear more than once in each graph for Figure 2.

AQ4: We have added an x-axis label in Figure 3. Please let me know if this is incorrect.

AQ5: The line for licorice in Figure 3 includes reference #10. Should this be reference #70?

PLEASE NOTE: Any changes to the figures must be made now. Changes at later stages are expensive and time-consuming and may result in the delay of your article's publication.

To avoid a delay, I would be grateful to receive a reply no later than Thursday, 1/31. Thank you for your help.

Best wishes,

Stephanie Casway, MA
Senior Production Editor
Obstetrics & Gynecology
American College of Obstetricians and Gynecologists
409 12th St, SW
Washington, DC 20024
Ph: (202) 314-2339
Fax: (202) 479-0830
scasway@greenjournal.org

The University of Aberdeen is a charity registered in Scotland, No SC013683.
Tha Oilthigh Obar Dheathain na charthannas clàraichte ann an Alba, Àir. SC013683.

The University of Aberdeen is a charity registered in Scotland, No SC013683.
Tha Oilthigh Obar Dheathain na charthannas clàraichte ann an Alba, Àir. SC013683.

The University of Aberdeen is a charity registered in Scotland, No SC013683.
Tha Oilthigh Obar Dheathain na charthannas clàraichte ann an Alba, Àir. SC013683.