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: Aug 22, 2019
To: "Benjamin B Albright" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-19-1396

RE: Manuscript Number ONG-19-1396

Gestational trophoblastic neoplasia following molar pregnancy: A systematic review and meta-analysis

Dear Dr. Albright:

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 Sep 12, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: The purpose of this manuscript is to "compare the cumulative incidence and pattern of GTN after reaching undetectable hCG following complete and partial molar pregnancy." This is a systematic review and meta-analysis of retrospective cohort studies.

1. In the paragraph starting on line 337-245, the authors propose recommendations for a more patient-friendly, reduced hcg testing, follow-up after the serum hCG is negative following evacuation in subjects with CM and PM. Do their recommendations vary depending on the frequency of GTN in the population of interest, eg. in Japanese or Native American patients with a molar pregnancy? Do their recommendations apply to specific countries?

2. Line 63 : "that results in". should it be "that occurs in"?

3. Line 74: "Obstetrics and Gynecology". Should it be Obstetricians and Gynecologists?

4. Line 120: "; (2) the study reported development of GTN..." Should it be (3)?

5. Please carefully review references and make sure they follow Instructions for authors for the Green Journal. egs. Please abbreviate American Journal of Obstetrics and Gynecology. For reference #4 please review reference format for ACOG Practice Bulletins.

6. In Table 1. The authors note CT by risk for a couple of the studies. Please define CT by risk in a footnote.

7. Do the authors have any data on how many of those subjects who developed GTN >6 months from undetectable sensitive serum hCG would have been detected by current urine hCG assays, both laboratory based and OTC urine hCGs? Could subjects after a negative serum hCG be followed with either OTC or laboratory-based urine hCGs?

8. Could the authors expand their discussion of the funnel plot for their primary outcome and the risk of publication bias?

Reviewer #2: Thank you for the opportunity to review the manuscript "Gestational trophoblastic neoplasia following molar pregnancy: A systematic review and meta-analysis". This paper is a meta-analysis of the literature published to date on gestational trophoblastic disease. The authors aimed to provide evidence-based follow-up recommendations for patients diagnosed with a partial or complete molar pregnancy.

The authors should be commended on their well written manuscript on a very rare disease. The authors had strict inclusion and exclusion criteria for the studies included in the meta-analysis and each study was vetted by 2 or more authors before inclusion. I have a few comments regarding the discussion of the article.

1. The authors suggest stratifying follow-up of patients with complete molar pregnancy by the time to first normal beta-HCG after uterine evacuation. They suggest that patients with beta normalization within 8 weeks have a low risk of recurrence and thus should be followed with one single additional beta 1 month after normalization. Can the authors commend further on other data which supports this? In their review of the papers included, did they find an average time to recurrence in these patients? Is 1 month better or would 3 months be better? I feel this conclusion is overstated given the data they present.

2. The authors suggest that patients with prolonged beta elevation (56 days or longer) should undergo prolonged screening up to one year. This contrasts with expert centers which recommend up to 6 months of screening only. The authors rationalize that 90% of recurrences occur in these patients with the majority of patients (60%) recurring after 6 months of follow-up. I am concerned that the studies included failed to identify new pregnancy events, hence the recurrence after 6 months could be related to a new pregnancy. Did the authors identify any other risk factors which could be associated with a late recurrence? I think this recommendation should be changed to "consider" screening these patients longer, with the need to further identify risks for development of GTN after 6 months of follow-up. For instance, do the other risk factors (age, size of original tumor, and pre-evacuation HCG) matter for these patients? I feel this recommendation is overstated and should be revised prior to acceptance.

Reviewer #3: This is a very well- written and comprehensive systematic review by Albright et al that explores an important question in relation to a rare disease. The authors determine the incidence of GTN after complete and partial molar pregnancies and determine that the rate of GTN after complete and partial molar pregnancies - they are able to validate prior incidence rates described in the literature. They also show that the incidence of GTN after undetectable HCG is very low and make a sound argument for reducing the frequency and duration of follow up. Rigorous methodology is used to arrive at conclusions. The results are nicely displayed in tables and flow chart. The manuscript is easy to read and results are highly likely to have an influence on general practice.
I would like to see further discussion on prior studies that advocate for less frequent screening after molar pregnancy, as some centers have already adopted this strategy. Description of GTD surveillance protocols used in large centers such as New England GTD center, Northwestern, and Charring Cross is worth discussing.

Reviewer #4: I appreciate the opportunity to review this systematic review and meta-analysis.
I would like to highlight some aspects that deserve modification.

The title of the paper ("Gestational trophoblastic neoplasia following molar pregnancy: A systematic review and meta-analysis") does not outline the exact dimension of the main objective of this study, which is to evaluate the development of gestational trophoblastic neoplasia (GTN) after reaching undetectable levels of human chorionic gonadotropin (hCG) following molar pregnancy. As it was presented, the title gives readers the impression that the authors will assess the risk of postmolar gestational trophoblastic neoplasia, which is not the primary goal of the authors.

It should be noted that the authors presented the overall risk of postmolar GTN as a secondary outcome based on the articles found using the strict search criteria of studies evaluating the development of GTN after reaching undetectable hCG following molar pregnancy. Therefore, the secondary results might not reflect the real incidence of the disease, since they are based on studies found using a search criteria of a very specific and rare situation in patients that developed GTN; not taking into account the majority of patients that develop GTN, which is before the normalization of hCG levels. To publication, I would suggest that the authors do not to include the study's secondary outcome of evaluating the overall incidence of GTN following molar pregnancy, not only this data are inopportune, but also out of context of the study's design and primary objective.

Throughout the text, the authors refer to "undetectable hCG". In fact this is a inaccurate laboratorial concept. The hCG tests have two types of reference values: the first one refers to the normal ranges of the test, which in the case of hCG, is generally levels below 5 IU/L (in a few laboratories, the reference would be below 2 IU/L); the second refers to the analytical sensitivity of the test, which is the ability of the test to detect the studied molecule, which in the vast majority of hCG tests reaches 0.1 IU/L. To state that hCG is undetectable indicates that the result is below the analytical sensitivity of the test. In post-molar follow-up, the goal is to achieve normal values - which represents remission of the disease. Therefore, I suggest that the authors substitute the expression "undetectable hCG" for "normal hCG levels".

In line 80, the authors presented "HCG" with H uppercase. But in endocrinology, the capital H refers to "hormone" (e.g.,

GH - growth hormone), while the small "h" refers to "human" (e.g., hCG - human chorionic gonadotropin).

In line 187, hCG unit is expressed in "UL/L", the correct being "IU/L".

In Table 1, the authors refer to the treatment of molar pregnancy in the article by Braga et al. as "Suction Curettage", while the vast majority of the other cited authors are referred to use "Uterine Evacuation". However, these techniques for treating molar pregnancy are the same. In a recent article, Padrón et al., under the guidance of Braga, (Padrón L, Rezende Filho J, Amim Junior J, Sun SY, Charry RC, Maestá I, Elias KM, Horowitz N, Braga A, Berkowitz RS. Manual Compared With Electric Vacuum Aspiration for Treatment of Molar Pregnancy. Obstet Gynecol. 2018 Apr;131(4):652-659.) describes in detail the uterine evacuation technique used in their Center, leaving no question that the procedure can also be referred as "Uterine evacuation".

STATISTICAL EDITOR COMMENTS:

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

Insert comments Fig 2A, 2 B/C, 3: These can be considerably abbreviated by eliminating the studies that have no contribution to the overall comparisons, ie, tthose that have Not estimable RRs, due to zero counts. Those NE entries can be separately entered in Tables or supplementary material to show how rates of neoplasia among each cohort were computed, but contribute nothing to the RRs.

Fig 2B: This figure has only two studies that contribute to the RR calculation. A sample of n = 2 is insufficient to estimate heterogeneity with any confidence. Should omit heterogeneity estimation.

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. These comments should be included in your point-by-point response cover letter.

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.

- This would be the American College of Obstetricians and Gynecologists.

- How does the long follow up cause infertility? Perhaps "Delayed child bearing"?

- were there any characteristics identified that were associated with higher risk of GTN?

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. 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.

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.

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

4. 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.

5. Have any of your figures been previously published in other sources?

Tables, figures, and supplemental digital content should be original. The use of borrowed material (eg, lengthy direct quotations, tables, figures, or videos) is discouraged, but should it be considered essential, written permission of the copyright holder must be obtained. Permission is also required for material that has been adapted or modified from another source.

Both print and electronic (online) rights must be obtained from the holder of the copyright (often the publisher, not the author), and credit to the original source must be included in your manuscript. Many publishers now have online systems for submitting permissions request; please consult the publisher directly for more information.

When you submit your revised manuscript, please upload 1) the permissions license and 2) a copy of the original source from which the material was reprinted, adapted, or modified (eg, scan of book page(s), PDF of journal article, etc.).

6. 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.

7. 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.

8. 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).

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: Reviews, 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. 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%").

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. The American College of Obstetricians and Gynecologists' (ACOG) documents are frequently updated. These documents may be withdrawn and replaced with newer, revised versions. If you cite ACOG documents in your manuscript, be sure the reference you are citing is still current and available. If the reference you are citing has been updated (ie, replaced by a newer version), please ensure that the new version supports whatever statement you are making in your manuscript and then update your reference list accordingly (exceptions could include manuscripts that address items of historical interest). If the reference you are citing has been withdrawn with no clear replacement, please contact the editorial office for assistance (obgyn@greenjournal.org). In most cases, if an ACOG document has been withdrawn, it should not be referenced in your manuscript (exceptions could include manuscripts that address items of historical interest). All ACOG documents (eg, Committee Opinions and Practice Bulletins) may be found via the Clinical Guidance & Publications page at https://www.acog.org/Clinical-Guidance-and-Publications/Search-Clinical-Guidance.

15. Table S.1 is actually a box. Please rename this s Box 1.

16. Figures

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

Please upload each figure as a separate file to Editorial Manager (do not embed the figure in your manuscript file).

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

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

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

***

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

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

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

Again, your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Sep 12, 2019, 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

Penn Medicine
University of Pennsylvania Health System

Dear Editors and Reviewers,

On behalf of my co-authors, I would like to thank you for considering our manuscript for publication in *Obstetrics & Gynecology*. We appreciate your thoughtful feedback and the opportunity to improve on our work. We hope the attached revised manuscript will meet the standard for publication. We are happy to continue to make further revisions as desired. Please see below for a point-by-point response to reviewer/editor comments with descriptions of revisions made in response.

I affirm 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 registered have been explained. MOOSE guidelines were followed and a checklist is enclosed. All authors meet the ICMJE standards for authorship credit, and do not have any conflicts of interest to report. Thank you for considering our work, and we look forward to hearing from you.

Sincerely,

Benjamin B. Albright, M.D., M.S.
[redacted]

Sarita Sonalkar, M.D., M.P.H.
[redacted]

REVIEWER COMMENTS:

Reviewer #1: The purpose of this manuscript is to "compare the cumulative incidence and pattern of GTN after reaching undetectable hCG following complete and partial molar pregnancy." This is a systematic review and meta-analysis of retrospective cohort studies.

1. In the paragraph starting on line 337-245, the authors propose recommendations for a more patient-friendly, reduced hCG testing; follow-up after the serum hCG is negative following evacuation in subjects with CM and PM. Do their recommendations vary depending on the frequency of GTN in the population of interest, e.g. in Japanese or Native American patients with a molar pregnancy? Do their recommendations apply to specific countries?
We did not differentiate our recommendations by race/ethnicity, as we have included all races/ethnicities in our search, and include studies from 6 different continents in our primary analysis. That being said, we have modified the section of the discussion including our recommendations for screening at the suggestion of this reviewer and Reviewer #2. We have softened our language from “recommendations” to “suggestions.” We have also added a qualifying sentence to that section that screening recommendations should be tailored to the local population, balancing the particular risk of disease with the costs and burdens of follow-up.

2. Line 63: "that results in". Should it be "that occurs in"?
We made this edit as described in line 63.

3. Line 74: "Obstetrics and Gynecology". Should it be Obstetricians and Gynecologists?
We made this edit as described in line 74.

4. Line 120: "; (2) the study reported development of GTN..." Should it be (3)?
We made this edit as described, now in line 119.

5. Please carefully review references and make sure they follow Instructions for authors for the Green Journal. E.g. please abbreviate American Journal of Obstetrics and Gynecology. For reference #4 please review reference format for ACOG Practice Bulletins.

We have reviewed and reformatted our reference as necessary to best reflect the requested reference formatting.

6. In Table 1. The authors note CT by risk for a couple of the studies. Please define CT by risk in a footnote.

We have added a footnote to Table 1 that clarifies “Certain patients given upfront chemotherapy for being “high risk,” see individual references for details.”

7. Do the authors have any data on how many of those subjects who developed GTN >6 months from undetectable sensitive serum hCG would have been detected by current urine hCG assays, both laboratory based and OTC urine hCGs? Could subjects after a negative serum hCG be followed with either OTC or laboratory-based urine hCGs?

We do not have data on exact levels of hCG with GTN diagnoses, but we appreciate this point about the potential of urine testing as a more accessible and less invasive/burdensome screening. We have added a sentence in the discussion to recognize this point in Lines 358-361, “Urine hCG surveillance is less well studied, but was represented in select included studies, and may offer a more accessible and less invasive and burdensome mode of surveillance that should be further validated in future research.”

8. Could the authors expand their discussion of the funnel plot for their primary outcome and the risk of publication bias?

We have added a sentence in our results section that references the funnel plot (Line 277-279). The funnel plot is designed to assess the relative risk estimate between complete versus partial molar pregnancy, but this value was of lesser importance as a

clinical outcome than the raw incidence estimates for complete and partial molar pregnancy, independent from each other.

Reviewer #2: Thank you for the opportunity to review the manuscript "Gestational trophoblastic neoplasia following molar pregnancy: A systematic review and meta-analysis". This paper is a meta-analysis of the literature published to date on gestational trophoblastic disease. The authors aimed to provide evidence-based follow-up recommendations for patients diagnosed with a partial or complete molar pregnancy.

The authors should be commended on their well-written manuscript on a very rare disease. The authors had strict inclusion and exclusion criteria for the studies included in the meta-analysis and each study was vetted by 2 or more authors before inclusion. I have a few comments regarding the discussion of the article.

1. The authors suggest stratifying follow-up of patients with complete molar pregnancy by the time to first normal beta-HCG after uterine evacuation. They suggest that patients with beta normalization within 8 weeks have a low risk of recurrence and thus should be followed with one single additional beta 1 month after normalization. Can the authors commend further on other data that supports this? In their review of the papers included, did they find an average time to recurrence in these patients? Is 1 month better or would 3 months be better? I feel this conclusion is overstated given the data they present.

In our discussion section paragraphs that address our suggestions for follow-up screening based on the data we present in the review (Lines 339-365), we describe that “given the low overall risk of GTN after normal hCG following complete mole of 0.35%, and that nearly 90% of these cases were diagnosed when time from evacuation to hCG normalization was 56 days (8 weeks) or longer, we similarly suggest that patients with complete mole with hCG normalization time less than 56 days could also safely exit

screening after a single confirmatory normal hCG." Unfortunately, we do not have more granular patient level data to address the average time from evacuation to normalization, if an alternative cut-off besides 56 days or 8 weeks would perform better, or how time from evacuation to normalization relates to time to GTN diagnosis. We added a statement to the limitations section in Lines 379-380 "sub-analyses are limited by the completeness and congruency of reported data across studies." Likely because of the emphasis of the 56-day threshold as a risk factor in the RCOG guidelines, some studies only reported data dichotomously around this specific threshold. We do appreciate this reviewers overall point that our wording of the recommendations may have been somewhat overstated in our original draft. We have modified the wording of this section to soften or recommendations to represent suggestions to consider for future guidelines, rather than a set of formal guidelines being suggested for adoption.

2. The authors suggest that patients with prolonged beta elevation (56 days or longer) should undergo prolonged screening up to one year. This contrasts with expert centers that recommend up to 6 months of screening only. The authors rationalize that 90% of recurrences occur in these patients with the majority of patients (60%) recurring after 6 months of follow-up. I am concerned that the studies included failed to identify new pregnancy events, hence the recurrence after 6 months could be related to a new pregnancy. Did the authors identify any other risk factors that could be associated with a late recurrence? I think this recommendation should be changed to "consider" screening these patients longer, with the need to further identify risks for development of GTN after 6 months of follow-up. For instance, do the other risk factors (age, size of original tumor, and pre-evacuation HCG) matter for these patients? I feel this recommendation is overstated and should be revised prior to acceptance.

We appreciate the reviewers concern that some of the late recurrences could have represented disease related to new pregnancy events rather than the index molar pregnancy. We have a statement in our limitations section that addresses this point in Lines 388-390 "Lastly, some of these cases remote from pregnancy could have been related to interval pregnancies, recognized or unrecognized, as most studies did not

compare the disease genetics with those of the index case of molar pregnancy." As mentioned elsewhere in this response, we do not have adequate data to compile and perform meta-analysis for certain risk factors associated with GTN after normal hCG or late cases after 6 months of normal hCG. As described previously, we have overall softened the wording of our discussion section on recommendations, and made them "suggestions for future screening guidelines." We are happy to further revise this aspect of our manuscript if desired by the editors/reviewers.

Reviewer #3: This is a very well written and comprehensive systematic review by Albright et al that explores an important question in relation to a rare disease. The authors determine the incidence of GTN after complete and partial molar pregnancies and determine that the rate of GTN after complete and partial molar pregnancies - they are able to validate prior incidence rates described in the literature. They also show that the incidence of GTN after undetectable HCG is very low and make a sound argument for reducing the frequency and duration of follow up. Rigorous methodology is used to arrive at conclusions. The results are nicely displayed in tables and flow chart. The manuscript is easy to read and results are highly likely to have an influence on general practice.

I would like to see further discussion on prior studies that advocate for less frequent screening after molar pregnancy, as some centers have already adopted this strategy. Description of GTD surveillance protocols used in large centers such as New England GTD center, Northwestern, and Charring Cross is worth discussing.

This topic is addressed in the discussion section paragraph spanning lines 325-337 of the revised manuscript. We describe recommendations from Charring Cross, the French Trophoblastic Disease Reference Center in Lyon, and the recently updated FIGO guidelines. We have added a sentence describing the recommendations from the New England Trophoblastic Disease Center (as published in UpToDate) to fortify this discussion in response to this comment.

Reviewer #4: I appreciate the opportunity to review this systematic review and meta-analysis.

I would like to highlight some aspects that deserve modification.

The title of the paper ("Gestational trophoblastic neoplasia following molar pregnancy: A systematic review and meta-analysis") does not outline the exact dimension of the main objective of this study, which is to evaluate the development of gestational trophoblastic neoplasia (GTN) after reaching undetectable levels of human chorionic gonadotropin (hCG) following molar pregnancy. As it was presented, the title gives readers the impression that the authors will assess the risk of postmolar gestational trophoblastic neoplasia, which is not the primary goal of the authors.
We have adjusted the title to “Gestational trophoblastic neoplasia after hCG normalization following molar pregnancy: A systematic review and meta-analysis” to more closely reflect our primary outcome in the study.

It should be noted that the authors presented the overall risk of postmolar GTN as a secondary outcome based on the articles found using the strict search criteria of studies evaluating the development of GTN after reaching undetectable hCG following molar pregnancy. Therefore, the secondary results might not reflect the real incidence of the disease, since they are based on studies found using a search criteria of a very specific and rare situation in patients that developed GTN; not taking into account the majority of patients that develop GTN, which is before the normalization of hCG levels. To publication, I would suggest that the authors do not to include the study's secondary outcome of evaluating the overall incidence of GTN following molar pregnancy, not only this data are inopportune, but also out of context of the study's design and primary objective.
We appreciate the feedback on this point. It is true that our primary intention with this study was to study the occurrence of GTN after normalization of hCG following molar

pregnancy. We felt this to be the most clinically relevant outcome due to the impact on screening recommendations. This outcome shaped our article selection criteria for the systematic review. However, we feel that the collected articles are representative of the cohort studies of molar pregnancy with the most robust follow up, and therefore least likely to understate the overall risk of GTN following molar pregnancy. Additionally, we did not find any prior systematic reviews of molar pregnancy, so this represents the first meta-analysis quantitative estimate of overall rates of GTN following molar pregnancy. We have edited the paragraph discussing this finding in the discussion (Lines 305-314) to make this point transparent and clear to the reader to allow him or her to interpret it as they see fit. It should also be noted that our estimate is generally consistent with commonly quoted estimates. If the collective reviewers and editors feel strongly that this secondary outcome should be excluded, we would be willing to do so in a future revision, but we feel it is a relevant and reportable finding.

Throughout the text, the authors refer to "undetectable hCG". In fact this is a inaccurate laboratorial concept. The hCG tests have two types of reference values: the first one refers to the normal ranges of the test, which in the case of hCG, is generally levels below 5 IU/L (in a few laboratories, the reference would be below 2 IU/L); the second refers to the analytical sensitivity of the test, which is the ability of the test to detect the studied molecule, which in the vast majority of hCG tests reaches 0.1 IU/L. To state that hCG is undetectable indicates that the result is below the analytical sensitivity of the test. In post-molar follow-up, the goal is to achieve normal values - which represents remission of the disease. Therefore, I suggest that the authors substitute the expression "undetectable hCG" for "normal hCG levels".

We appreciate this comment. We had actually gone back and forth amongst ourselves as co-authors as to which terminology to use, as both have been represented in the literature. We appreciate your argument for the use of the term “normal” and we have made this adjustment throughout the manuscript.

In line 80, the authors presented "HCG" with H uppercase. But in endocrinology,

the capital H refers to "hormone" (e.g., GH - growth hormone), while the small "h" refers to "human" (e.g., hCG - human chorionic gonadotropin).
We made this edit as suggested in line 80.

In line 187, hCG unit is expressed in "UL/L", the correct being "IU/L".
We made this edit as suggested, now in line 185-186.

In Table 1, the authors refer to the treatment of molar pregnancy in the article by Braga et al. as "Suction Curettage", while the vast majority of the other cited authors are referred to use "Uterine Evacuation". However, these techniques for treating molar pregnancy are the same. In a recent article, Padrón et al., under the guidance of Braga, (Padrón L, Rezende Filho J, Amim Junior J, Sun SY, Charry RC, Maestá I, Elias KM, Horowitz N, Braga A, Berkowitz RS. Manual Compared With Electric Vacuum Aspiration for Treatment of Molar Pregnancy. Obstet Gynecol. 2018 Apr;131(4):652-659.) describes in detail the uterine evacuation technique used in their Center, leaving no question that the procedure can also be referred as "Uterine evacuation".
We have made this edit as suggested in Table 1.

STATISTICAL EDITOR COMMENTS:

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

Insert comments Fig 2A, 2 B/C, 3: These can be considerably abbreviated by eliminating the studies that have no contribution to the overall comparisons, ie, those that have Not estimable RRs, due to zero counts. Those NE entries can be separately entered in Tables or supplementary material to show how rates of neoplasia among each cohort were computed, but contribute nothing to the RRs.
We feel that the presentation of all studies in this figure is essential. The relative risk finding between complete and partial molar pregnancy is a secondary finding. The more relevant data in this figure are the raw numbers of cases of molar pregnancy

(denominator) and numbers of cases of GTN (numerator), so that the reader may see how much each study contributed to the sums that comprise the binomial proportions that are the primary incidence estimates of GTN. Without including all studies in this figure, the reader would be confused as to how the different studies contributed to the overall estimates presented in the manuscript text.

Fig 2B: This figure has only two studies that contribute to the RR calculation. A sample of n = 2 is insufficient to estimate heterogeneity with any confidence. Should omit heterogeneity estimation.

We have erased the presentation of heterogeneity from this sub-figure as suggested. We do not put much emphasis on the heterogeneity estimates, because they are not particularly relevant to this meta-analysis, which is focused less on the comparison between complete and partial molar pregnancy, and more on the overall estimates of GTN incidence for each independently.

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. These comments should be included in your point-by-point response cover letter.

- Line 74. This would be the American College of Obstetricians and Gynecologists.

We made this edit as suggested in Line 74.

- Line 90. How does the long follow up cause infertility? Perhaps "Delayed child bearing"?

We made this edit as suggested, now in Line 89.

- Line 267. Were there any characteristics identified that were associated with higher risk of GTN?

Unfortunately, there was inadequate reporting of patient characteristics across included studies to compile data to assess characteristics, such as age, sex, parity, etc. with risk of GTN. A statement was added to our limitations section that addresses this point in Lines 388-390 “Lastly, some of these cases remote from pregnancy could have been related to interval pregnancies, recognized or unrecognized, as most studies did not compare the disease genetics with those of the index case of molar pregnancy.”

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

A. OPT-IN: Yes, please publish my point-by-point response letter.

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

We select choice A.

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

The disclosures are correct as written (we have none).

4. 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.
This statement is included in the opening page of this document.

5. Have any of your figures been previously published in other sources?
No

6. 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.
We have no problems with the reVITALize definitions.

7. 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.

Our manuscript adheres to these length requirements with 3,726 words of text in the body of the manuscript, and 25 pages of material including excluding references and online supplemental material.

8. Specific rules govern the use of acknowledgments in the journal. Please note the following guidelines:

*** All financial support of the study must be acknowledged.**

We have no financial support to report.

*** 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.**

We received no assistance with manuscript preparation.

*** 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.**

We acknowledged the support of a biomedical librarian, Melanie Cedrone, who received no funding for her participation and gave written permission to be named.

*** 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).**

Our manuscript and the contained data have not been presented at any meetings.

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

The abstract for our manuscript has a word count of 296 words, excluding section headers. We have used the journal's recommended headers for systematic reviews.

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.

We have utilized standard abbreviations and acronyms. In our manuscript text, we have additionally chosen to, after spelling out wit the first use, abbreviate the phrases complete mole (CM), partial mole (PM), and gestational trophoblastic neoplasia (GTN) as each is represented frequently throughout the manuscript. If this is not considered acceptable, we can edit the text to write out these phrases with each use.

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.

All such constructs have been edited out of the manuscript.

12. 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%").
We have attempted to follow these guidelines in our reporting.

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.
We have attempted to follow the table guidelines as stated.

14. The American College of Obstetricians and Gynecologists' (ACOG) documents are frequently updated. These documents may be withdrawn and replaced with newer, revised versions. If you cite ACOG documents in your manuscript, be sure the reference you are citing is still current and available. If the reference you are citing has been updated (ie, replaced by a newer version), please ensure that the new version supports whatever statement you are making in your manuscript and then update your reference list accordingly (exceptions could include manuscripts that address items of historical interest). If the reference you are citing has been withdrawn with no clear replacement, please contact the editorial office for assistance (obgyn@greenjournal.org). In most cases, if an ACOG document has been withdrawn, it should not be referenced in your manuscript (exceptions could include manuscripts that address items of historical interest). All ACOG documents (eg, Committee Opinions and Practice Bulletins) may be found via the Clinical Guidance & Publications page at https://www.acog.org/Clinical-Guidance-and-Publications/Search-Clinical-Guidance.
In our manuscript, we reference a withdrawn ACOG practice bulletin on Molar Pregnancy as a means of explaining how screening recommendations have evolved

more recently. We recognize in the text that the document has been withdrawn and subsequently reference the 2018 FIGO guidelines, to which ACOG now defers according to the catalog of ACOG Practice Bulletins.

15. Table S.1 is actually a box. Please rename this s Box 1.
This change has been made.

16. Figures. When you submit your revision, art saved in a digital format should accompany it. If your figure was created in Microsoft Word, Microsoft Excel, or Microsoft PowerPoint formats, please submit your original source file. Image files should not be copied and pasted into Microsoft Word or Microsoft PowerPoint. Please upload each figure as a separate file to Editorial Manager (do not embed the figure in your manuscript file). If the figures were created using a statistical program (eg, STATA, SPSS, SAS), please submit PDF or EPS files generated directly from the statistical program.
We have submitted PDF formatted files containing our figures separate from our manuscript file.

17. 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.
We will consider this if accepted.