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: Oct 15, 2020
To: "John Tunnicliff Soper" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-20-2539

RE: Manuscript Number ONG-20-2539

Gestational Trophoblastic Disease: Current evaluation and management

Dear Dr. Soper:

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 14 days from the date of this letter. If we have not heard from you by Oct 29, 2020, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1:

The manuscript presented is a clinical expert series on Gestational Trophoblastic Disease. The manuscript is thorough, but the author needs to maintain consistency in the naming of the different types of GTD. The terms can be confusing, and it would be optimal to remain clear throughout the manuscript.

1. Abstract: Line 53 is likely a misspelling "mohydatidiform moles…"

2. Lines 101-105: is there some estimate of the sensitivities of these different presenting symptoms for GTD?

3. Lines 125-127: please give a little more information on NLRP7 and KHDC3L. It is interesting to know that these have a normal chromosomal complement. Having an understanding that NLRP7 is a maternal effect gene can help to understand this difference.

4. Line 140: I believe this should be partial mole.

5. Lines 172-173: Recommend adding at the end of this sentence "as a baseline if pulmonary complications arise." Pulmonary complications are described in more detail later, but this will better introduce that topic.

6. Lines 173-174: In the text it states that TFTs should be obtained if hyperthyroidism is clinically suspected, but the table states it should be obtained if the uterus is >14-16 weeks. Please clarify the recommendation.

7. Line 190: remove the duplicative sentence "This reduces the chance of perforation".

8. Lines 190-191: could you please describe the data behind the recommendation for IV oxytocin for several hours after evacuation? Is this for all types of patients or maybe just those considered higher risk? What about other agents (cytotec, etc.)?

9. Line 194: Is there an estimate on the incidence of pulmonary complications?

10. Line 212: By how much is the risk of post-molar GTN reduced with hysterectomy compared to D&E?

11. Lines 223-224: for additional testing after hCG normalizes, the text refers to table 3, and table 3 refers to the text. Recommend just giving a recommendation for additional monitoring for complete moles in the table and leaving the

explanation for potential variability in the text.

12. Lines 255-257: what kind of patients (inclusion/exclusion criteria) were involved in this evaluation?

13. Lines 292-294: This is unclear. Does it mean that in patients who underwent a second D&E and had persistent histologic evidence of GTD? If they didn't have a second D&E, was the persistent histologic evidence from an endometrial pipelle?

14. I would recommend moving the section "Diagnosis and Pretherapy Evaluation" to before the section "Histology of GTN".

15. Lines 314-315: This is where the terminology is confusing. The term proliferative moles without myometrial invasion refers to post-molar GTN? If so, please use the consistent term. The difference between post-molar GTN and invasive mole is still unclear after reading this. Is a hysterectomy specimen required to make this differentiation?

16. Line 385-387 is confusing. At different dilutions of patient serum, the phantom hCG should reveal consistent results, but the sentence reads "will not yield". Consider removing this sentence entirely as the following sentence expresses the idea more clearly.

17. Move sentence 402 to immediately after sentence 394-395 for clarity.

18. Move subheading (management of high-risk metastases) to line 483.

19. Line 520: how successful is pembrolizumab in these cases?

20. Line 527: I believe the heading should read "surveillance after treatment for gestational trophoblastic neoplasia"

Reviewer #2:

Thank you for the opportunity to review this manuscript "Gestational Trophoblastic Disease: Current evaluation and management". In this manuscript the author thoroughly reviews the treatment and management of gestational trophoblastic disease. The paper is well written and comprehensive. I would suggest that the paper is reviewed for grammatical errors; I have included a few below in my review.

1. Line 53: the term mohydatidiform was used. I think this should be hydatidiform.

2. Line 56: The word "complicatsions" is spelled incorrectly.

3. Line 158: reference number in this line splits the word uteri

4. Line 240-242: This area is a little confusing. In the lines prior to this the author states that patients that do not need chemo with a complete mole can be followed for 6 months while those with a partial mole only need one confirmatory beta hcg. In this section they are discussing the use of contraception and the need to be on reliable contraception for a year. This is a bit confusing and should be corrected to state that the patient should be on contraception for the period of surveillance. Please reword for clarity.

5. Line 373: In this section the author is discussing the need for imaging while undergoing work-up for GTN. The author states that a chest xray can miss small chest metastasis. Patients with small chest metastasis could be at risk for brain metastasis. They recommend only getting a brain MRI if the patient has chest disease. I am unclear if the author is suggesting that all patients get a CXR, CT of the abd/pelvis, and brain MRI or CT chest/abd/pelvis and only get the MRI of the brain if there is chest disease. I think data would support CT chest/abd/pelvis and imaging of the head only if there is chest disease. Please clarify.

6. Line 387: There is an extra period in this line.

7. Line 437: The author states that patients with low risk disease require only one cycle of chemotherapy past normalization of the beta. I am not aware of data that supports this approach. Most data recommends 2-3 cycles past normalization. NCCN guidelines also recommend 2-3 cycles. I think this should be corrected to correlate with NCCN guidelines.

8. Line 449: In this paragraph the author discusses the treatment of patients that plateau or have an increased beta-hcg while undergoing chemotherapy. The author suggests that if the beta has not decreased by at least 10% in one cycle a change in regimen is recommended. The author also discusses that if there is a rise, the regimen should be changed. Does the author have a reference for this? Patients that have a slow decrease or an increase are at increased risk of failing the

regimen, however, at this time the recommendations are to wait for the patient to have a plateau over 3 cycles (6 weeks) or an increase over 2 cycles (4 weeks) before changing the regimen. The author may have anecdotal data or maybe there is a publication I am not aware of. Please change this to agree with current guidelines or add a citation to back this up.

9. Line 454: The author discusses a second option for single agent treatment is carboplatin. This is based on one series of 21 patients. The regimen was well tolerated. Carboplatin has not been compared to methotrexate or actinomycin-d in this setting. Although I think it is a reasonable alternative based on this trial, I do not think we can safely substitute carboplatin for either of the other medications. Please add additional discussion on this point.

10. Line 542-543: In an older study patients treated for GTN had an increased risk of second malignancy. The hazard ratio was 1.5. This was a survey based study and did not take into account other risk factors for malignancy. Please include a state about the potential biases found in this study.

11. Line 554: In the treatment of PSTT and ETT, the preferred regimen is EMA-EP or TE/TP not EMA-CO. Please change this recommendation.

12. There is a bit of discussion in the paper about management of subsequent pregnancy and recommendation for early ultrasound. Could the author comment on any need for pathologic examination of the placenta or need for post-partum hcg. These are older recommendations that I think are still around but lack evidence.

13. It is possibly outside the scope of this paper, but I think additional discussion on the use of immunotherapy in the treatment of GTN would be interesting. I would suggest a short paragraph about the future direction of the treatment of GTN.

Reviewer #3:

1. This is Clinical Expert Series review of gestational trophoblastic disease, describing current evaluation and management of molar pregnancy and gestational trophoblastic neoplasia. Through a comprehensive and updated review of the literature, the author provides an overview of these disease entities, including diagnostic parameters, appropriate workup, and current recommendations for treatment. The main take home message is that most women diagnosed with molar pregnancy or gestational trophoblastic neoplasia can be cured, with fertility preservation, as long as they are managed appropriately.

2. The author provides updated management and treatment recommendations that were published in the last couple of years, some of which differ from prior strategies (ie, how long to monitor hCG after molar pregnancy, and nuances of front-line management of low risk GTN). There is also information on the molecular characteristics of trophoblastic tumors, and presence of germline mutations seen in women with recurrent molar pregnancies. This is novel information and should be expanded upon. Specifically, would recommend that the author specify "germline" mutations in line 125 and expand upon this topic. Additional recommendations for this section: Lines 125-127 is a 2-sentence paragraph, please expand or reorganize within paragraph included in lines 128-134. Line 128, should be paternally not parentally.

3. This is an excellent topic for the Clinical Expert Series. This is a topic that is confusing to trainees and some generalist providers. This manuscript provides a well-organized reference for management of GTD and GTN.

4. Additionally, there have been important changes in treatment of GTN that are highlighted in this paper. However, there are many typos and grammatical errors such that it made assessing the content difficult (ie, lines 53, 55, 56, 61, 77, 80, 123, 158, 192, 193, 196 plus more). There are also areas where the writing style could be more concise (eliminate sentence fragments) or organized to make the concepts more understandable, for example line 167-175. This is a lengthy manuscript, which is appropriate for such a large topic, making concise writing of utmost importance.

5. The content of the abstract, figures, and tables is complementary to the manuscript. Specifically, in table 2 consider adding paternal vs. paternal/maternal karyotype origin, delete or define quantifiers (often, usually, slight-moderate, etc), clarify conflicting percentage of risk of postmolar GTN when compared to text. In table 3, clarify when thyroid function tests should be tested (table says when uterus is > 14 weeks, text says if clinically suspected. Clarify which clotting studies should be obtained.

6. References are complete. Please add entire reference for #45.

EDITORIAL OFFICE COMMENTS:

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

2. Obstetrics & Gynecology uses an "electronic Copyright Transfer Agreement" (eCTA). When you are ready to revise your manuscript, you will be prompted in Editorial Manager (EM) to click on "Revise Submission." Doing so will launch the resubmission process, and you will be walked through the various questions that comprise the eCTA. Each of your coauthors will receive an email from the system requesting that they review and electronically sign the eCTA.

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

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

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

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 data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-obstetrics-data-definitions and the gynecology data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-gynecology-data-definitions. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

5. 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).

6. Provide a short title of no more than 45 characters (40 characters for case reports), including spaces, for use as a running foot.

7. 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. Please provide a word count.

8. 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.

9. 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.

10. Your manuscript contains a priority claim. 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 it is not based on a systematic search but only on your level of awareness, it is not a claim we permit.

11. Please relabel Tables 1, 4, and 5 as "Box 1," "Box 2," and "Box 3?" Please also renumber the remaining tables accordingly.

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.

12. Please review examples of our current reference style at http://ong.editorialmanager.com (click on the Home button in the Menu bar and then "Reference Formatting Instructions" document under "Files and Resources). Include the digital object identifier (DOI) with any journal article references and an accessed date with website references. Unpublished data, in-press items, personal communications, letters to the editor, theses, package inserts, submissions, meeting presentations, and abstracts may be included in the text but not in the reference list.

In addition, 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 at the Clinical Guidance page at https://www.acog.org/clinical (click on "Clinical Guidance" at the top).

13. Figures 1-6: Please upload a second version of each image without text or arrows. These will be added back per journal style.

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

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

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

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

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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. Do not omit your responses to the Editorial Office or Editors' comments.

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

Again, your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Oct 29, 2020, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

John O. Schorge, MD
Associate Editor, Gynecology

2019 IMPACT FACTOR: 5.524
2019 IMPACT FACTOR RANKING: 6th out of 82 ob/gyn journals

_____

[redacted]

Editorial staff, *Obstetrics and Gynecology*

RE: Revisions Manuscript Number ONG-20-2539

Gestational Trophoblastic Disease: Current evaluation and management

To whom it may concern:

I have down-loaded a revised manuscript, referenced above for consideration for publication in *Obstetrics and Gynecology*. In this revised manuscript, I have formatted the tables in the word table format, changed tables that were outlines into "Boxes", and submitted figures in labeled tiff format with no markings on the images. I added a short title to the title page, to be used as a running footer. The manuscript is submitted in "track changes" format to reflect the changes that were made in response to the reviewers' comments, and I will address each reviewer's comments below.

I would like to apologize to the original reviewers: I inadvertently down-loaded a copy of the manuscript that had not been proof-read for spelling in my original submission and was chagrinned to see the manuscript that you had to review. I assure you that mistake is not repeated.

Reviewer #1:

The manuscript presented is a clinical expert series on Gestational Trophoblastic Disease. The manuscript is thorough, but the author needs to maintain consistency in the naming of the different types of GTD. The terms can be confusing, and it would be optimal to remain clear throughout the manuscript.

Terminology is consistent throughout.

1. Abstract: Line 53 is likely a misspelling "mohydatidiform moles…" Misspelling is corrected in the revised manuscript.

2. Lines 101-105: is there some estimate of the sensitivities of these different presenting symptoms for GTD?

I noted that the classical presentation of abnormal bleeding haad decreased in the series reported by Sun et al from 84% to 46% during the course of their study.

3. Lines 125-127: please give a little more information on NLRP7 and KHDC3L. It is interesting to know that these have a normal chromosomal complement. Having an understanding that NLRP7 is a maternal effect gene can help to understand this difference.

I expanded the discussion of NLRP7 and KHDC3L germline mutations.

4. Line 140: I believe this should be partial mole.

Corrected

5. Lines 172-173: Recommend adding at the end of this sentence "as a baseline if pulmonary complications arise." Pulmonary complications are described in more detail later, but this will better introduce that topic.

I made this change.

6. Lines 173-174: In the text it states that TFTs should be obtained if hyperthyroidism is clinically suspected, but the table states it should be obtained if the uterus is >14-16 weeks. Please clarify the recommendation.

I changed the wording in the Table (now Box 2) to conform to the text.

7. Line 190: remove the duplicative sentence "This reduces the chance of perforation".

I removed the duplicative sentence.

8. Lines 190-191: could you please describe the data behind the recommendation for IV oxytocin for several hours after evacuation? Is this for all types of patients or maybe just those considered higher risk? What about other agents (cytotec, etc.)?

Our institutional practice is to administer Pitocin. I recognized that other oxytocics could be used.

9. Line 194: Is there an estimate on the incidence of pulmonary complications?

I noted that overall incidence of pulmonary complications was 1%, increasing to approximately 20% in patients with large uteri.

10. Line 212: By how much is the risk of post-molar GTN reduced with hysterectomy compared to D&E?

The risk of postmolar GTN after hysterectomy is referenced as 3-5%, compared with a risk of 15 – 20% after D&E.

11. Lines 223-224: for additional testing after hCG normalizes, the text refers to table 3, and table 3 refers to the text. Recommend just giving a recommendation for additional

monitoring for complete moles in the table and leaving the explanation for potential variability in the text.

Done- I discussed FIGO and NCCN recommendations in text.

12. Lines 255-257: what kind of patients (inclusion/exclusion criteria) were involved in this evaluation?

I commented that two of the three studies evaluated only high-risk moles, while one included low-risk moles.

13. Lines 292-294: This is unclear. Does it mean that in patients who underwent a second D&E and had persistent histologic evidence of GTD? If they didn't have a second D&E, was the persistent histologic evidence from an endometrial pipelle?

I specified that this was tissue obtained at repeat curettage.

14. I would recommend moving the section "Diagnosis and Pretherapy Evaluation" to before the section "Histology of GTN".

I debated moving these sections, but chose to leave them in place.

15. Lines 314-315: This is where the terminology is confusing. The term proliferative moles without myometrial invasion refers to post-molar GTN? If so, please use the consistent term. The difference between post-molar GTN and invasive mole is still unclear after reading this. Is a hysterectomy specimen required to make this differentiation?

A histological diagnosis or at least radiologic evidence of direct myometrial invasion is needed to fit the strict diagnosis of invasive mole. I am aware of instances where a hysterectomy was performed for postmolar GTN diagnosed by rising hCG values and no myometrial invasion was noted on the pathology specimen. I specified that proliferative moles have no evidence of myometrial invasion and yet are treated on the basis of hCG value.

16. Line 385-387 is confusing. At different dilutions of patient serum, the phantom hCG should reveal consistent results, but the sentence reads "will not yield". Consider removing this sentence entirely as the following sentence expresses the idea more clearly.

This is clarified. I was combining serial dilutions and using different assays in a single sentence and have broken these out.

17. Move sentence 402 to immediately after sentence 394-395 for clarity.

Sentence moved

18. Move subheading (management of high-risk metastases) to line 483.

Subheading relocated

19. Line 520: how successful is pembrolizumab in these cases?

I detailed the 5 patients who have been reported in print.

20. Line 527: I believe the heading should read "surveillance after treatment for gestational trophoblastic neoplasia"

The heading title is changed

Reviewer #2:

Thank you for the opportunity to review this manuscript "Gestational Trophoblastic Disease: Current evaluation and management". In this manuscript the author thoroughly reviews the treatment and management of gestational trophoblastic disease. The paper is well written and comprehensive. I would suggest that the paper is reviewed for grammatical errors; I have included a few below in my review.

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2. Line 56: The word "complicatsions" is spelled incorrectly.
   Corrected

3. Line 158: reference number in this line splits the word uteri
   Corrected

4. Line 240-242: This area is a little confusing. In the lines prior to this the author states that patients that do not need chemo with a complete mole can be followed for 6 months while those with a partial mole only need one confirmatory beta hcg. In this section they are discussing the use of contraception and the need to be on reliable contraception for a year. This is a bit confusing and should be corrected to state that the patient should be on contraception for the period of surveillance. Please reword for clarity.

   I changed this section to reflect in slightly more detail the recommendations for hCG surveillance. The need for contraception was specified to be during the time of hCG surveillance.

5. Line 373: In this section the author is discussing the need for imaging while undergoing work-up for GTN. The author states that a chest xray can miss small chest metastasis. Patients with small chest metastasis could be at risk for brain metastasis. They recommend only getting a brain MRI if the patient has chest disease. I am unclear if the author is suggesting that all patients get a CXR, CT of the abd/pelvis, and brain MRI or CT chest/abd/pelvis and only get the MRI of the brain if there is chest disease. I think data would support CT chest/abd/pelvis and imaging of the head only if there is chest disease. Please clarify.

   I clarified; "Brain MRI or CT scans with contrast should be performed in any patient with pulmonary metastases or neurological symptoms."

6. Line 387: There is an extra period in this line.

   Removed

7. Line 437: The author states that patients with low risk disease require only one cycle of chemotherapy past normalization of the beta. I am not aware of data that supports this approach. Most data recommends 2-3 cycles past normalization. NCCN guidelines also recommend 2-3 cycles. I think this should be corrected to correlate with NCCN guidelines.

   I expanded the discussion on the use of consolidation therapy. Surwit and Hammond reported 3% recurrence after one cycle for low-risk GTN, similar to the 3.8% recurrence rate noted by the New England Trophoblastic Disease Center among 288 patients who received no consolidation. I then discussed the retrospective study between the UK and Netherlands groups comparing 2 cycles (8.3% relapse rate) vs 3 cycles (4.0% relapse rate). Unfortunately, these are all retrospective single-institutional studies. I do reference the FIGO and NCCN recommendation for 2 – 3 cycles of consolidation. I did not editorialize in this article about the issue of making strong NCCN guidelines, but I believe that a definitive study has yet to be initiated.

8. Line 449: In this paragraph the author discusses the treatment of patients that plateau or have an increased beta-hcg while undergoing chemotherapy. The author suggests that if the beta has not decreased by at least 10% in one cycle a change in regimen is recommended. The author also discusses that if there is a rise, the regimen should be changed. Does the author have a reference for this? Patients that have a slow decrease or an increase are at increased risk of failing the regimen, however, at this time the recommendations are to wait for the patient to have a plateau over 3 cycles (6 weeks) or an increase over 2 cycles (4 weeks) before changing the regimen. The author may have anecdotal data or maybe there is a publication I am not aware of. Please change this to agree with current guidelines or add a citation to back this up.

I changed this to reflect the NCCN current guidelines, although they are different from published guidelines used in studies reported from Charing Cross or even the GOG in the MTX/ACT-D trial (three hCG values with decline <10%).

9. Line 454: The author discusses a second option for single agent treatment is carboplatin. This is based on one series of 21 patients. The regimen was well tolerated. Carboplatin has not been compared to methotrexate or actinomycin-d in this setting. Although I think it is a reasonable alternative based on this trial, I do not think we can safely substitute carboplatin for either of the other medications. Please add additional discussion on this point.

   I indicated the numbers of patients treated and that more study is needed.

10. Line 542-543: In an older study patients treated for GTN had an increased risk of second malignancy. The hazard ratio was 1.5. This was a survey based study and did not take into account other risk factors for malignancy. Please include a state about the potential biases found in this study.

    I updated the reference and noted that this was a survey study. Also discussed early menopause in the EMA/CO patients, but not single-agent therapy.

11. Line 554: In the treatment of PSTT and ETT, the preferred regimen is EMA-EP or TE/TP not EMA-CO. Please change this recommendation.
    Unfortunately, very little data for these rare tumors. I changed the chemotherapy to EMA/EP, TE/TP and multi-day etoposide-platin regimens.

12. There is a bit of discussion in the paper about management of subsequent pregnancy and recommendation for early ultrasound. Could the author comment on any need for pathologic examination of the placenta or need for post-partum hcg. These are older recommendations that I think are still around but lack evidence.

    I commented that these are often recommended, but I do not know of any studies that evaluated the utility of these practices.

13. It is possibly outside the scope of this paper, but I think additional discussion on the use of immunotherapy in the treatment of GTN would be interesting. I would suggest a short paragraph about the future direction of the treatment of GTN.

    I expanded the section on immunotherapy. The intended readership comprises general OB-Gyns, OB-Gyn residents and Gynecologic Oncologists or Fellows who aren't exposed to a lot of patients with these diseases. For this reason, I didn't go into salvage therapies in much depth.

Reviewer #3:

1. This is Clinical Expert Series review of gestational trophoblastic disease, describing current evaluation and management of molar pregnancy and gestational trophoblastic neoplasia. Through a comprehensive and updated review of the literature, the author provides an overview of these disease entities, including diagnostic parameters, appropriate workup, and current recommendations for treatment. The main take home message is that most women diagnosed with molar pregnancy or gestational trophoblastic neoplasia can be cured, with fertility preservation, as long as they are managed appropriately.

   Thank you

2. The author provides updated management and treatment recommendations that were published in the last couple of years, some of which differ from prior strategies (ie, how long to monitor hCG after molar pregnancy, and nuances of front-line management of low risk GTN). There is also information on the molecular characteristics of trophoblastic tumors, and presence of germline mutations seen in women with recurrent molar pregnancies. This is novel information and should be expanded upon. Specifically, would recommend that the author specify "germline" mutations in line 125 and expand upon this topic. Additional recommendations for this section: Lines 125-127 is a 2-sentence paragraph, please expand or reorganize within paragraph included in lines 128-134. Line 128, should be paternally not parentally.

   I specified germ-line mutations and expanded upon the topic. Eliminated the two sentence paragraph. Corrected the misspelling.

3. This is an excellent topic for the Clinical Expert Series. This is a topic that is confusing to trainees and some generalist providers. This manuscript provides a well-organized reference for management of GTD and GTN.

   Thank you

4. Additionally, there have been important changes in treatment of GTN that are highlighted in this paper. However, there are many typos and grammatical errors such that it made assessing the content difficult (ie, lines 53, 55, 56, 61, 77, 80, 123, 158, 192, 193, 196 plus more). There are also areas where the writing style could be more concise (eliminate sentence fragments) or organized to make the concepts more understandable, for example line 167-175. This is a lengthy manuscript, which is appropriate for such a large topic, making concise writing of utmost importance.

   I corrected misspellings, “cleaned up” and tightened up sentence structure throughout.

5. The content of the abstract, figures, and tables is complementary to the manuscript. Specifically, in table 2 consider adding paternal vs. paternal/maternal karyotype origin, delete or define quantifiers (often, usually, slight-moderate, etc), clarify conflicting percentage of risk of postmolar GTN when compared to text. In table 3, clarify when thyroid function tests should be tested (table says when uterus is > 14 weeks, text says if clinically suspected. Clarify which clotting studies should be obtained.

   In the Table, I specified paternal and maternal chromosomal compliments and tightened up the estimates of GTN. The recommendation for TFTs is consistent (when hyperthyroidism is suspected). P

6. References are complete. Please add entire reference for #45.

   Corrected

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I changed the tables that were presented as outlines into “Box” form and renumbered other tables accordingly.

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Sincerely, John Soper, MD