

OBSTETRICS & GYNECOLOGY



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- Comments from the reviewers and editors (email to author requesting revisions)
- Response from the author (cover letter submitted with revised manuscript)*
- Email correspondence between the editorial office and the authors*

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

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

Questions about these materials may be directed to the *Obstetrics & Gynecology* editorial office:

obgyn@greenjournal.org.

Date: Jan 04, 2019
To: "Helena C. van Doorn" [REDACTED]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-18-2316

RE: Manuscript Number ONG-18-2316

The Impact of Second Uterine Curettage on the Number of Chemotherapy Courses in Low-risk Postmolar Gestational Trophoblastic Neoplasia. A Single-Centre, Randomized Controlled Study

Dear Dr. van Doorn:

Your manuscript has been reviewed by the Editorial Board and by special expert referees. Although it is judged not acceptable for publication in Obstetrics & Gynecology in its present form, we would be willing to give further consideration to a revised version.

If you wish to consider revising your manuscript, you will first need to study carefully the enclosed reports submitted by the referees and editors. Each point raised requires a response, by either revising your manuscript or making a clear and convincing argument as to why no revision is needed. To facilitate our review, we prefer that the cover letter include the comments made by the reviewers and the editor followed by your response. The revised manuscript should indicate the position of all changes made. We suggest that you use the "track changes" feature in your word processing software to do so (rather than strikethrough or underline formatting).

Your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Jan 25, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

REVIEWER #1:

In this manuscript, the authors present a randomized trial comparing single vs. second uterine curettage on the number of chemotherapy treatments administered among women with a low-risk molar GTN. The study is relevant as there have been some conflicting results as to the utility of second curettage in this clinical context. The randomized design is inherently the best approach to sorting out the conflict. I am unclear what is the connection between the Netherlands and Egypt and the sequence from patient presentation to subject consent and study enrollment is not very clear. As noted by the authors, at least one of the issues raised in the second-curettage approach is that it may obviate the need for chemotherapy, yet this study design cannot address this question. I have the following specific comments/questions:

- 1) I think the introduction needs some tweaking. The second paragraph sets up the study question but the first paragraph should better introduce the general problem and management of GTN. For a general OB/GYN audience, it may not be clear the role and timing of chemotherapy and thus arriving at the 2nd paragraph the reader may not be sure where the curettage question fits. Also, always put a comma before "which" when you're using it as an alternative for "that" (or just use "that" instead).
- 2) You need to state a clearer (as in direction of effect) study aim OR a hypothesis in your introduction. In your methods you describe a power analysis but that power analysis depends on what you're trying to prove. If second-curettage is better than single-curettage that's a different question than an equivalence trial, thus insofar as it appears you did the former state as much in a hypothesis that concludes your introduction.
- 3) As noted above it is not entirely clear how patients got into this study. There is a site in Egypt that sees a bunch of patients and everyone with a mole was either enrolled or excluded - that's how it reads. That seems kind of odd insofar as I don't commonly see everyone voluntarily enroll in a trial. When was the consent done?
- 4) You need to state the range of sizes your random blocks varied between.
- 5) How was allocation assignment concealed to the researchers? If a researcher really believed in second-curettage and they knew the allocation for a given patient was for single-curettage your sampling is busted.
- 6) Can more be said about the web-based system that generated the allocation sequence?
- 7) One possible matter to discuss is the differences (if any) in a curettage done using a traditional suction machine and a

MVA. I suspect most US D&Cs in this context are done in the OR with a suction machine thus the efficacy - possibly seen in the one US trial - may relate to how the D&C was done.

8) Line 161 - you expected to find the reduction as a result of the 2-curettage technique? Be more specific. It should be noted that a drop in number of chemotherapy treatments from 5 to 4 or 3 is still notable yet your study power would have been inadequate to demonstrate that change. What is the minimal number of chemotherapy treatments that is important?

9) I respect your use of more conservative (non-parametric) statistics. I wonder, however, why? If you're using a random sample shouldn't the number of chemotherapy treatments be normal distributed and thus a simple t-test would work?

10) Line 236 - The sentence starting in this line doesn't make sense (and it ends in a preposition). I think, as I said above, it would be helpful to understand the time sequence of chemotherapy and curettage. How do these usually fit together with or without the second-curettage.

Overall, the study has merit but there are some details to nail down.

REVIEWER #2:

I congratulate the authors on carrying out a well-designed, randomized trial evaluating the efficacy of a second curettage in patients with a diagnosis of low-risk (presumed non-metastatic) postmolar gestational trophoblastic neoplasia. Unlike some other trials, all patients received chemotherapy so there was no definitive measure of the curative potential of the second curettage, although the second curettage did not result in fewer courses of methotrexate chemotherapy to achieve hCG normalization. The only factor which was found to affect number of courses of chemotherapy required to achieve hCG normalization was hCG level both as a continuous variable and high (>1500-5,000) vs low (<1,500). Specifically, uterine bleeding and volume of tissue within the uterus as estimated by ultrasound were not predictive of number of courses of chemotherapy required to reach hCG normalization nor success of initial methotrexate chemotherapy.

Abstract

Objectives:

1. define GTN (gestational trophoblastic neoplasia)

Methods:

- 2- In a phase III trial, patients with low-risk postmolar GTN...
- 3- Delete β here and elsewhere in the manuscript
- 4- Why did the authors limit the eligibility criteria to patients with hCG level ≤ 5000 IU/L?

Results:

5. Between October 2011 and February 2016, 89 eligible patients were enrolled in the study, 86 of whom (43 in each group) were eventually included in the intention to treat analysis

Conclusion:

6. Second uterine curettage had no impact...

Introduction:

7. Postmolar gestational trophoblastic neoplasia (GTN) is typically diagnosed in asymptomatic women undergoing serum human chorionic gonadotropin (hCG) monitoring after evacuation of a complete or partial molar pregnancy. 1,2 Following the diagnosis of postmolar GTN based on International Federation of Gynecology and Obstetrics (FIGO) criteria, 3 patients at low-risk for failure of single-agent chemotherapy (FIGO score 0-6) can be treated with methotrexate or actinomycin D resulting in complete response rates of 70-80% and survival rates approaching 100%. 4,5

8. Line 94: Two prospective observational studies have been published. A small...

9. Line 96: A study performed...

10. Line 99: infection and bleeding, as well as a delay...

Materials and Methods:

11. Line 115: 18 or over with postmolar GTN, a FIGO score <7 , a serum hCG level $\leq 5,000$ IU/L,...

12. Line 125: How were the levels of hCG chosen - both for inclusion in the study and then for randomization?

13. Line 139: What was the value of "normal" hCG?

Results:

14. Line 183 & 188: fulfill is misspelled

Discussion:

15. The second sentence doesn't make sense and is grammatically incorrect

16. Line 242: In the prospective...

17. Line 259: correlate with the hCG level...

Table 1

18. FIGO score (Interestingly, no patient had a FIGO score >2, due almost certainly to eliminating all patients with postmolar GTN who had an hCG > 5,000 IU/L. Why did the authors exclude these patients from the study?

19. hCG level Not β hCG. Need to define below table

20. Weight units (kilograms)

Table 2

21. Histology of 2nd curettage was not choriocarcinoma in one patient. That was noted in a subsequent pregnancy.

REVIEWER #3:

Review of an article for Gyn Oncology by Hemida et al

The enclosed article by Hemida et al represents the first prospective randomized study to evaluate whether a second uterine curettage when a patient presents with a low risk post molar gestational trophoblastic neoplasia (GTN) reduces the number of courses of subsequent chemotherapy. The study found that performing a second D&C did not influence the number of subsequent courses of chemotherapy to achieve remission and as the authors point out this is consistent with another study that was not a prospective randomized trial (reference 14, Growdon et al Gynecol Oncol 2009). This study therefore does make an important contribution to patient management. However, prior to publication I would like to point out certain issues with the paper that could be substantially strengthened.

1. The data that is presented in tables 3, 4 and 5 could be presented with a greater degree of clarity. Further clarity could be explained by further explanation in the Materials and Methods section, Results section, or potentially as footnotes at the base of the table 5. For example, on lines 229-231 the authors describe that the success rate of methotrexate treatment is similar in both treatment groups and refer to table 5. I do not find data related to this result shown in table 5. Perhaps it would be useful to have a statistical consultant look at the manuscript with particular attention to the representation of the data in tables 3, 4 and 5.

2. On line 140 the authors indicate that "two consolidation courses of methotrexate were given." Lybol et al in 2012 published in Gynecologic Oncology in a study from data from both Holland and United Kingdom that 3 courses of consolidation chemotherapy versus 2 courses were more effective in reducing the risk of relapse. Why did the authors choose 2 courses of chemotherapy for consolidation?

3. On lines 115 and 116 the authors indicate participants had a "WHO low or intermediate risk score". It would be reasonable for the authors to simply state what that would be in terms of a risk score.

4. The authors do point out that if the antecedent pregnancy was a complete molar pregnancy versus a partial molar pregnancy that may influence the number of courses of chemotherapy required to achieve remission. The authors indicate that they did not have the tissues from all the patients from the antecedent molar pregnancy. However, for the tissues that were available it would be interesting and useful if the two treatment groups had comparable percentages of complete versus partial molar pregnancy. Even if the data were incomplete the information could still be informative.

STATISTICAL EDITOR'S COMMENTS:

1. Abstract: Should conform to our usual template for RCTs and include a brief summary of criteria for calculating sample

size for primary outcome.

2. lines 161-164: Need to include the estimate for the expected SD or pooled SD for the number of chemo courses. From the power and other data supplied, appears to be SD ~ 2.5 , with mean difference of 2.3 courses.

3. Table 1: Since this was a randomized trial, there is no need to statistically compare the two groups. Need to provide units for weight and BMI. For uterine mass, mm³ is a unit of volume, not mass.

4. Table 2: Should clearly separate the primary outcome from the others.

5. Tables 3, 4: These may be of interest to the reader, but again need to demarcate from the primary outcome (# of chemo courses needed to normalize β hCG level).

6. Tables 4, 5: Need to clarify whether these are crude ORs, or adjusted, and if so, then should include a column for crude, then adjusted ORs and cite in footnote which variables were retained in the final model.

EDITORIAL OFFICE COMMENTS:

1. The Editors of Obstetrics & Gynecology are seeking to increase transparency around its peer-review process, in line with efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online. Additionally, unless you choose to opt out, we will also be including your point-by-point response to the revision letter, as well as subsequent author queries. If you opt out of including your response, only the revision letter will be posted. Please reply to this letter with one of two responses:

1. OPT-IN: Yes, please publish my response letter and subsequent email correspondence related to author queries.
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2. As of December 17, 2018, Obstetrics & Gynecology has implemented an "electronic Copyright Transfer Agreement" (eCTA) and will no longer be collecting author agreement forms. When you are ready to revise your manuscript, you will be prompted in Editorial Manager (EM) to click on "Revise Submission." Doing so will launch the resubmission process, and you will be walked through the various questions that comprise the eCTA. Each of your coauthors will receive an email from the system requesting that they review and electronically sign the eCTA.

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

3. Clinical trials submitted to the journal as of July 1, 2018, must include a data sharing statement. The statement should indicate 1) whether individual deidentified participant data (including data dictionaries) will be shared; 2) what data in particular will be shared; 3) whether additional, related documents will be available (eg, study protocol, statistical analysis plan, etc.); 4) when the data will become available and for how long; and 5) by what access criteria data will be shared (including with whom, for what types of analyses, and by what mechanism). Responses to the five bullet points should be provided in a box at the end of the Methods section.

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

5. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Original Research reports should not exceed 26 typed, double-spaced pages (6,500 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and print appendixes) but exclude references.

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

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

* All financial support of the study must be acknowledged.

* Any and all manuscript preparation assistance, including but not limited to topic development, data collection, analysis, writing, or editorial assistance, must be disclosed in the acknowledgments. Such acknowledgments must identify the entities that provided and paid for this assistance, whether directly or indirectly.

* All persons who contributed to the work reported in the manuscript, but not sufficiently to be authors, must be acknowledged. Written permission must be obtained from all individuals named in the acknowledgments, as readers may infer their endorsement of the data and conclusions. Please note that your response in the journal's electronic author form verifies that permission has been obtained from all named persons.

* If all or part of the paper was presented at the Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists or at any other organizational meeting, that presentation should be noted (include the exact dates and location of the meeting).

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

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

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

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

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

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

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

Again, your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Jan 25, 2019, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

The Editors of Obstetrics & Gynecology

2017 IMPACT FACTOR: 4.982

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

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



Cancer Institute

To:

Nancy C. Chescheir, MD

Chapel Hill, NC

Editor-in-Chief Obstetrics and Gynecology

January 19th, 2019

RE: Manuscript number ONG-18-2316

Dear Editor,

We would like to thank the referees and the editors for their efforts to study our manuscript and give valuable comments. Herewith we submit a revised version for further consideration regarding acceptability for publication.

Answers to the reviewers comments are given point to point.

REVIEWER #1:

1) I think the introduction needs some tweaking. The second paragraph sets up the study question but the first paragraph should better introduce the general problem and management of GTN. For a general OB/GYN audience, it may not be clear the role and timing of chemotherapy and thus arriving at the 2nd paragraph the reader may not sure where the curettage question fits. Also, always put a comma before "which" when you're using as an alternative for "that" (or just use "that" instead).

Response. The first and second reviewer both made some suggestions to rewrite the first paragraph. We re-wrote this section such that the a bit more details in the preamble of the paper are given, keeping the comments of both reviewers in our mind:

The original text was: "Gestational trophoblastic neoplasia (GTN) includes postmolar GTN, which is typically diagnosed in asymptomatic women undergoing routine serum hCG monitoring after evacuation of a complete or partial molar pregnancy. Following diagnosis of postmolar GTN, staging and risk assessment (mostly using FIGO staging and the modified World Health Organisation (WHO) Prognostic Scoring System as adapted by FIGO) distinguishes patients at low versus high-risk, which influences subsequent decisions on the specific chemotherapy regimen. At present, most low-risk (WHO risk score 0–6) GTN patients are treated with single-agent methotrexate or actinomycin D, and remission rates of 90% and over are obtained in stage I disease, compared to rates of approximately 70% in stage II and stage III disease.

To be replaced by: lines 84 - 97.

"Postmolar gestational trophoblastic neoplasia (GTN), is typically diagnosed in asymptomatic women undergoing serum human chorionic gonadotropin (hCG) monitoring after evacuation of a complete or partial molar pregnancy. Following diagnosis of postmolar GTN, firstly risk classification is carried out, based on International Federation of Gynecology and Obstetrics (FIGO) criteria. Patients at low-risk for failure of single-agent chemotherapy (FIGO score <7) can be treated with methotrexate or actinomycin D monotherapy, resulting in complete response rates of 70-80% and survival rates approaching 100%. Single agent chemotherapy is started shortly after diagnoses and monitored with hCG levels. When the chosen regimen fails second line treatment is started, most likely another chemotherapy regimen.

- Thanks for the advice on the use of a comma before "which".

2) You need to state a clearer (as in direction of effect) study aim OR a hypothesis in your introduction. In your methods you describe a power analysis but that power analysis depends on what you're trying to prove. If second-curettage is better than single-curettage that's a different question than an equivalence trial, thus insofar as it appears you did the former state as much in a hypothesis that concludes your introduction.

Response. We did not perform an equivalence trial, but expected to reduce the number of chemotherapy courses by two in the study arm. We have adjusted the last paragraph expecting that this clarifies our expectations. lines 111 - 117.

"Based on previous studies we hypothesised that a second curettage reduces the number of chemotherapy courses needed to normalize the hCG level by two courses, hence reduce treatment time by four weeks. So, this single-centre, randomized phase III trial in low-risk postmolar GTN patients investigated whether second uterine curettage reduced the number of chemotherapy courses needed to achieve hCG normalisation, and diminish toxicity and relapse rates, or not. Subsequently we aimed to identify variables associated with the number of courses required."

3) As noted above it is not entirely clear how patients got into this study. There is a site in Egypt that sees a bunch of patients and everyone with a mole was either enrolled or excluded - that's how it reads. That seems kind of odd insofar as I don't commonly see everyone voluntarily enroll in a trial. When was the consent done?

Response. As written in the body of the text The Mansoura University Hospital provides tertiary healthcare for most of the Delta region of Egypt, with a population of about 12 million. Incidence of GTN is high in this region, although very precise numbers are lacking. The first author is the founder of the first Gestational Trophoblastic Clinic (GTC) in Egypt, and the lead of GTD management team of Mansoura University. Patients with GTN are referred to this clinic from the entire region. Women visiting the GTC were admitted to the hospital to complete the investigations and start treatment. The first counseling session at the clinic was of the patient

and her peers with the treating physician in the presence of a nurse. Information about the disease, standard treatment, and the study were shared. Subsequently written information was provided, this consisted of a general information leaflet in Arabic on GTN as well as a patient information form on the study. (added in the manuscript line 130) We can provide these when wanted. After reading the information the patient was given time to ask questions and considerate participation. When she agreed the consent form was signed. After randomization (details see below) the patient was informed about the allocated treatment, and asked again if she wanted to proceed in the study.

In Figure 1, and in the results section we describe that a total of 97 patients were eligible, finally 86 were included in the intention to treat analyses; five eligible patients refused randomization, and two started treatment in another hospital (more details in the body of the paper). After randomization one chose hysterectomy in another hospital, one refused subsequent treatment after methotrexate failure. We think this reflects a fair and strict policy.

Prior to study-submission the patients were not informed that treatment would be provided free of charge, since this might have influenced their choice, particularly for the less fortunate women. Therefore we moved the statement regarding costs to the end of this section, lines 133-135.

4) You need to state the range of sizes your random blocks varied between.

Response. In the original text we wrote that a block randomization was performed. We have to apologize that this was not correct, since a minimization procedure was used. In the new document this has been adjusted. lines 139 - 144.

"Random assignments to second curettage or not (1:1) were balanced with use of a biased-coin minimization procedure, with the bias dependent on the average imbalance between numbers of patients already assigned to each treatment arm overall and within the stratification factors of the new patient. Patients were randomly assigned via Trial Online Process, a Web-based application, managed by the research centre of the Erasmus MC Cancer Institute, University Medical Centre Rotterdam, the Netherlands. The patients were stratified according to the presence or absence of vaginal bleeding and the level of baseline serum hCG, i.e., < 1,500 IU/L or 1,500-5,000 IU/L, since previous studies suggested that these factors might influence the effect of second curettage. The assigned treatment arm was sent immediately via e-mail to the treating gynecologist." line 147.

5) How was allocation assignment concealed to the researchers? If a researcher really believed in second-curettage and they knew the allocation for a given patient was for single-curettage your sampling is busted.

Response. Allocation assignment was done by the web-based application "Trial Online Process", managed by a the research center located at the Erasmus MC Cancer Clinic, Erasmus University Rotterdam, The Netherlands. The assigned treatment arm was sent immediately via e-mail to

the treating gynecologist. (line 147) So, the clinician did not have a role in treatment selection. We can show a copy of such an email for clarification.

6) Can more be said about the web-based system that generated the allocation sequence?

Response. The Web-based application is called the "Trial Online Process". (line 139-140) Statisticians of the research center of the ErasmusMC used this for many studies for the Hemato-Oncology Cooperative (HOVON) study group. For an example see Sonneveld P et al. J Clin Oncol 30:2946-2955. This service was financially sponsored by the last author of the manuscript (HvD).

7) One possible matter to discuss is the differences (if any) in a curettage done using a traditional suction machine and a MVA. I suspect most US D&Cs in this context are done in the OR with a suction machine thus the efficacy - possibly seen in the one US trial - may relate to how the D&C was done.

Response. Although the assumption that a traditional suction machine is superior to MVA in evacuating the uterine cavity is understandable, this belief is not supported by any research. In practice MVA is easy to use and particularly there is no problem to gain a continuous negative suction pressure. We would like to refer to other authors that state similarly: [11, 12] "MVA is a safe and effective alternative of conventional electric vacuum aspiration. It is superior to electric vacuum aspiration in terms of reduced cost and need for general anaesthesia and is thus useful at low resource setting with scarcity of electricity and general anaesthesia".

In the mentioned US trial of Osborne et al. [10] the method of evacuation was not specified, and it could include intra-operative ultrasound localization of residual trophoblastic tissue or directed hysteroscopic resection. Patients could have had either or both procedures as well as no imaging guided procedure. In our study all evacuations were performed in a uniform way, under ultrasound guidance, by a gynecologist with extensive experience with these procedures. We therefore think that the lack of effect of the second curettage is not related to the use of a MVA.

8) Line 161 - you expected to find the reduction as a result of the 2-curettage technique? Be more specific. It should be noted that a drop in number of chemotherapy treatments from 5 to 4 or 3 is still notable yet your study power would have been inadequate to demonstrate that change. What is the minimal number of chemotherapy treatments that is important?

Response We changed the first sentence of the discussion to make it more specific: "From this randomized study we conclude that second uterine curettage does not significantly reduce the number of chemotherapy courses in patients with postmolar GTN" lines 273 - 274 Also in the abstract we changed the conclusion to: "Second uterine curettage did not reduce the number of chemotherapy courses required, or affect relapse rate in low-risk postmolar GTN patients." lines 77 - 79.

The question "what is the minimal number of chemotherapy treatments that is important?" is interesting, but not quite easy to answer. We are not aware of publications that answer this question from the perspective of the post-molar GTN patient. Lesser chemotherapy treatment does reduce treatment time, side effects of chemotherapy will subside earlier, and the moment to resume pregnancy will come sooner. Although we did not encounter complications of the second curettage they have been reported by others. An answer to the question should take all of these aspects into account. Since we did not find a reduction in the number of courses we plead against second curettage, unless the effect of such procedure on hCG levels is awaited for.

9) I respect your use of more conservative (non-parametric) statistics. I wonder, however, why? If you're using a random sample shouldn't the number of chemotherapy treatments be normal distributed and thus a simple t-test would work?

Response. We agree that when using a random sample of the population it can sometimes be expected to be normally distributed, for example in case of BMI. However, we do not agree that this can be assumed for the number of chemotherapy treatments generally used for this post-molar GTN. Descriptive analysis showed a distribution slightly skewed to the right (not included in manuscript). Moreover, it is widely accepted to reserve parametric statistics for sample sizes above 100 patients. We believe readers will appreciate a more conservative non-parametric test over a T-test with more power to show statistical differences in data that might fail to meet the T-test' assumptions. If strongly encouraged, however, we could test the data for these assumptions and apply parametric tests where possible.

10) Line 236 - The sentence starting in this line doesn't make sense (and it ends in a preposition). I think, as I said above, it would be helpful to understand the time sequence of chemotherapy and curettage. How do these usually fit together with or without the second-curettage.

Response. The mentioned sentence was deleted. The patients in the study arm (second curettage) had their first methotrexate injection within 24 hours after the suction curettage. We added this to the text in the methods section (line 160 - 161)

REVIEWER #2:

Abstract

Objectives: 1. define GTN (gestational trophoblastic neoplasia)

Response. Done accordingly

Methods: 2- In a phase III trial, patients with low-risk postmolar GTN...

Response. "or intermediate" was deleted.

3- Delete β here and elsewhere in the manuscript

Response. “β” was removed.

4- Why did the authors limit the eligibility criteria to patients with hCG level ≤ 5000 IU/L?

Response. We limited the eligibility criteria to patients with hCG level ≤ 5000 IU/L in accordance with the UK guidelines, this was clarified in the discussion section (line 296)

“In the United Kingdom women with persisting disease are only considered for repeat uterine evacuation when the hCG is less than 5,000 IU/ L, and ultrasound imaging suggests that the disease is confined to the uterine cavity” [15]

Results:

5. Between October 2011 and February 2016, 89 eligible patients were enrolled in the study, 86 of whom (43 in each group) were eventually included in the intention to treat analysis.

Response. We agree with the reviewer that this sentence would be preferred. However, in the submission phase of the study the editors requested us to add information on the relation between the start of the inclusion and the moment the study was published at the Dutch trial register.

For this reason we started the results section of the abstract with: "October 17th, 2011 the first patient was enrolled. Five patients were enrolled prior to the trial registration (March 12th, 2012), 89 eligible patients entered the study, finally in each group 43 patients were included in the intention to treat analyses." (40 words)

Since words are limited and, to our sincere believe, we have only a very short interval between these two dates, we would like to argue that this information is not crucial and should only be added to the body of the text. We added this information to the results section (lines 223 - 225)

Conclusion: 6. Second uterine curettage had no impact...

Response. “has” was changed to “had”.

Introduction:

7. Postmolar gestational trophoblastic neoplasia (GTN) is typically diagnosed in asymptomatic women undergoing serum human chorionic gonadotropin (hCG) monitoring after evacuation of a complete or partial molar pregnancy. Following the diagnosis of postmolar GTN based on International Federation of Gynecology and Obstetrics (FIGO) criteria, patients at low-risk for failure of single-agent chemotherapy (FIGO score 0-6) can be treated with methotrexate or actinomycin D resulting in complete response rates of 70-80% and survival rates approaching 100%.

Response. The paragraph was re-edited. Also the suggestion of the 1st reviewer on the timing of chemotherapy is added in this section. (lines 160 - 161)

8. Line 94: Two prospective observational studies have been published. A small...

Response. The paragraph was re-edited.

9. Line 96: A study performed...

Response. The sentence was modified.

10. Line 99: infection and bleeding, as well as a delay...

Response. The sentence was modified.

Materials and Methods:

11. Line 115: 18 or over with postmolar GTN, a FIGO score <7, a serum hCG level $\leq 5,000$ IU/L,...

Response. The sentence was modified.

12. Line 125: How were the levels of hCG chosen - both for inclusion in the study and then for randomization?

Response. The level of hCG ($\leq 5,000$ IU/L) was chosen in accordance with the UK guideline, that suggests this as upper level for second curettage in postmolar GTN [15]. In previous studies it was suggested that the hCG level would correlate with treatment success, therefore we stratified between less than 1,500 and 1,500 - 5,000 to ensure that such effect would become clear. The GOG study [10] also used this levels in sub analyses "If the registration hCG level was between 100 and 1,500 mIU/mL then surgical cure was reported in 53%, when it was between 1,500 and 5,000 mIU/mL surgical cure was observed in 40%" .

13. Line 139: What was the value of "normal" hCG?

Response. hCG < 7 IU/L, we added this value (line 163)

Results: 14. Line 183 & 188: fulfill is misspelled

Response. The paper is written in UK English. Outside North America fulfil is the preferred spelling. We hope the editors agree that we re-write the paper to US English after final acceptance.

Discussion: 15. The second sentence doesn't make sense and is grammatically incorrect

Response. This sentence was deleted.

16. Line 242: In the prospective...

Response. We changed the text accordingly.

17. Line 259: correlate with the hCG level...

Response. We changed the text accordingly.

Table 1

18. FIGO score (Interestingly, no patient had a FIGO score >2, due almost certainly to eliminating all patients with postmolar GTN who had an hCG > 5,000 IU/L. Why did the authors exclude these patients from the study?

Response. See response to Q12.

19. hCG level Not β hCG. Need to define below table

Response. " β " was deleted and the abbreviation hCG was defined in the footing of the table.

20. Weight units (kilograms)

Response. Units were added.

Table 2

21. Histology of 2nd curettage was not choriocarcinoma in one patient. That was noted in a subsequent pregnancy.

Response. This is addressed in the footing of the table.

REVIEWER #3:

1. The data that is presented in tables 3, 4 and 5 could be presented with a greater degree of clarity. Further clarity could be explained by further explanation in the Materials and Methods section, Results section, or potentially as footnotes at the base of the table 5. For example, on lines 229-231 the authors describe that the success rate of methotrexate treatment is similar in both treatment groups and refer to table 5. I do not find data related to this result shown in table 5. Perhaps it would be useful to have a statistical consultant look at the manuscript with particular attention to the representation of the data in tables 3, 4 and 5.

Response. For clarification, in the statistical analyses paragraph, we explained the statistical analysis used in the same order as the results appear in Table 1-5. To improve clarity we choose to report the variables in the first column for Table 3-5 as categorical variables only, these are more useful in clinic and give more clinical information.

We altered the tables and hope the reviewer agrees with the following modifications:

Table 3:

- Renamed "Subgroup analyses for the mean number of chemotherapy courses needed to achieve hCG normalization"

- The numbers (eg., (28/23) for vaginal bleeding) were removed from the first column since they can also be found in Table 1.

- In the footnote of Table 3 we added "listed as mean number, with the standard deviation between brackets"

- "histology" was moved from Table 3 to Table 1.

Table 4:

- Title changed to "Univariable linear regression analysis showing the effect on total number of chemotherapy courses needed to achieve hCG normalization".

- to clarify that the randomization arms have been compared, we wrote in the first column and first row, "second curettage and methotrexate versus methotrexate"

- high (1,500 - 5,000 IU/L versus low (<1,500IU/L) rather than high versus low

Table 5:

- title has been changed into "Table 5. Univariable logistic regression showing the effect on treatment success.

- high (1,500 - 5,000 IU/L versus low (<1,500IU/L) rather than high versus low

- The footnote has been altered into Successful treatment is defined as reaching normalization of serum hCG level using methotrexate alone, without need for emergency surgery and with uneventful follow-up. This was achieved by 36 out of 43 cases in the control group, and 37 out of 43 cases in the intervention group.

2. On line 140 the authors indicate that "two consolidation courses of methotrexate were given." Lybol et al in 2012 published in Gynecologic Oncology in a study from data from both Holland and United Kingdom that 3 courses of consolidation chemotherapy versus 2 courses were more effective in reducing the risk of relapse. Why did the authors choose 2 courses of chemotherapy for consolidation?

Response. The mentioned study is a retrospective analysis of patients from 1980 to 2008 and in the authors recommended a RCT to confirm their findings. Moreover, at the time we speak the Dutch guideline (updated in 2018) still advises 2 consolidation courses in low risk post molar GTN. It is interesting that one of the authors of the Lybol paper was co-author of this Dutch guideline.

3. On lines 115 and 116 the authors indicate participants had a "WHO low or intermediate risk score". It would be reasonable for the authors to simply state what that would be in terms of a risk score.

Response. The sentence was changed to "a FIGO score <7"

4. The authors do point out that if the antecedent pregnancy was a complete molar pregnancy versus a partial molar pregnancy that may influence the number of courses of chemotherapy required to achieve remission. The authors indicate that they did not have the tissues from all the patients from the antecedent molar pregnancy. However, for the tissues that were available it would be interesting and useful if the two treatment groups had comparable percentages of complete versus partial molar pregnancy. Even if the data were incomplete the information could still be informative.

Response. We agree with the reviewer that it would be very interesting, but to differentiate partial mole from complete mole P57 and genotyping are mandatory in difficult cases. These are costly tests and not used or available in our pathology laboratory. Therefore we decided to exclude the type of antecedent molar pregnancy from analysis to avoid reporting incorrect results. This point was clarified in the "limitations of the study" section.

STATISTICAL EDITOR:

1. Abstract: Should conform to our usual template for RCTs and include a brief summary of criteria for calculating sample size for primary outcome.

Response. The abstract was re-edited, and criteria for sample size calculation were added. line 61

2. lines 161-164: Need to include the estimate for the expected SD or pooled SD for the number of chemo courses. From the power and other data supplied, appears to be SD ~ 2.5, with mean difference of 2.3 courses.

Response. Based on previously published data, we expected to find a mean reduction from 4.8 to 2.5 courses chemotherapy courses with an expected SD of 2.4, before hCG normalization. lines 187 - 188.

3. Table 1: Since this was a randomized trial, there is no need to statistically compare the two groups. Need to provide units for weight and BMI. For uterine mass, mm³ is a unit of volume, not mass.

Response. Although comparing is not strictly needed we prefer to give these data. When the reviewer thinks we should delete them we are willing to do so. Units for weight and BMI are added. We changed uterine mass into uterine lesion.

4. Table 2: Should clearly separate the primary outcome from the others.

Response. We added "primary outcome" and "secondary outcome" to the table.

5. Tables 3, 4: These may be of interest to the reader, but again need to demarcate from the primary outcome (# of chemo courses needed to normalize β hCG level).

Response. We changed the titles for clarification, see reply to reviewer 3. We can add the primary outcome to Table 3, but are not certain whether the reviewer thinks that would be appropriate, since this can be found in Table 2. In Table 4 we inserted an empty row below the primary outcome and changed the content of the first column from curettage into "Second curettage and methotrexate versus methotrexate".

6. Tables 4, 5: Need to clarify whether these are crude ORs, or adjusted, and if so, then should include a column for crude, then adjusted ORs and cite in footnote which variables were retained in the final model.

Response In Tables 4 and 5 the results of univariate analyses are given. When imputing the results of our study in a multivariate model only hCG level related to the number of chemotherapy courses. This result is noted in the results section. (line 255)

EDITORIAL OFFICE:

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. (..)

Response 1.OPT-IN: Yes, please publish my response letter and subsequent email correspondence related to author queries.

3. Clinical trials submitted to the journal as of July 1, 2018, must include a data sharing statement. The statement should indicate 1) whether individual deidentified participant data (including data dictionaries) will be shared; 2) what data in particular will be shared; 3) whether additional, related documents will be available (eg, study protocol, statistical analysis plan, etc.); 4) when the data will become available and for how long; and 5) by what access criteria data will be shared (including with whom, for what types of analyses, and by what mechanism). Responses to the five bullet points should be provided in a box at the end of the Methods section.

Response We are not yet familiar with the details that you request. We added lines 207 - 212): "De-identified participant data on patient level and related documents (e.g., study protocol) are available for sharing. Requests can be addressed to H.C. van Doorn at h.vandoorn@erasmusmc.nl. In general, requests made by physicians and epidemiologists for research, teaching, and clinical purposes will be granted in a timely matter and shared in a secured way obeying our hospital policies." When possible we would like to see an example who the journal want us to write the "box".

4. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, (..)

Response We adhere to the reVITALize definitions.

5. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Original Research reports should not exceed 26 typed, double-spaced pages (6,500 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, *references*, tables, boxes, figure legends, and print appendixes) but *exclude references*.

Response Including the pages with references the length is 28 pages, without references it is 24 pages. Subheadings (abstract, introduction etc all started on a new page. Each Tables (a total of 5) is given a new page. Word count is 290 for the abstract and 5474 for the whole text including abstract and references.

6. Titles in Obstetrics & Gynecology are limited to 100 characters (including spaces). (..)

Response The original title with 138 characters was shortened to 93 characters.

original: The Impact of Second Uterine Curettage on the Number of Chemotherapy Courses in Low-risk Postmolar Gestational Trophoblastic Neoplasia. A Single-Centre, Randomized Controlled Study.

new: Second Curettage and the Number of Chemotherapy Courses in Postmolar Gestational Trophoblastic Neoplasia. A Single-Centre, Randomized Controlled Study.

7. Specific rules govern the use of acknowledgments in the journal. Please note the following guidelines:(..)

Response Acknowledgement has been checked

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

Response In order to obey to this word limits we removed the following from the abstract:

"The patients were stratified for hCG level and vaginal bleeding."and "Groups were comparable with regard to demographics and patient characteristics."

We also would like to replace (see comment reviewer 2, Q 5) "October 17th, 2011 the first patient was enrolled. Five patients were enrolled prior to the trial registration (March 12th, 2012), 89 eligible patients entered the study, finally in each group 43 patients were included in the intention to treat analyses." (40 words) by "Between October 2011 and February 2016, 89 eligible patients were enrolled in the study, 86 of whom (43 in each group) were eventually included in the intention to treat analysis." (30 words) In the body of the text the information on enrolment prior to registration was added.

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

Response Some alterations were made

12. Please review the journal's Table Checklist to make sure that your tables conform to journal style. The Table Checklist is available online [here](#).

Response The checklist was used

Daniel Mosier

From: H.C. van Doorn [REDACTED]
Sent: Tuesday, February 5, 2019 9:14 AM
To: Daniel Mosier
Cc: reda elshouky [REDACTED]
Subject: RE: Manuscript Revisions: ONG-18-2316R1
Attachments: 18-2316R1 ms (2-4-19v2) comm LD.docx

Dear dr Mosier,

Thank you for this. We are very happy to get this news.

1. Please note the minor edits and deletions throughout. Please let us know if you disagree with any of these changes.

In the boxes in the manuscript comments are placed.

“Single agent chemotherapy is started shortly after diagnoses and monitored with hCG levels. When the chosen regimen fails second line treatment is started, most likely another chemotherapy regimen. “ was removed: This line was added after the first revision: the reviewer asked us to explore this since he or she felt that the audience of the journal would like to get a bit more background.

Line 11: use debulking of the uterus: “Uterus” might not be the appropriate word; as a non- native English person I read this as if part of the uterus is removed. It is about the intrauterine content. When it is technically correct I think this can be rephrased this way

2. LINE 30: Drs. El-Deek, Toson, and Burger will need to complete our electronic Copyright Transfer Agreement, which was sent to them through Editorial Manager.

I contacted them. Professor Burger will be able to do so next Friday, he is currently on annual leave and has no internet available till Friday.

3. LINE 39: The running title provided was too long. Do you agree with the shortened version?

Line 1: Title was changed; I suppose the word second remains?

Line 39: We agree with the shorter version

4. LINE 44: Are you able to be more specific about how she contributed?

Dr Seynaeve read an earlier version and gave valuable advice on language. Later we decided on a medical editor as well.

5. LINE 87 (Deleted Text): This sentence would be confusing to the readership

In the commentary I also wrote that anatomical staging is a new concept for me. I am not sure what this is?

6. LINE 107: This is actually the WHO score, but for a largely OBGYN and international audience it is best to simplify were possible.

Agree

7. LINE 185: Here is the box you mention in your response to reviewers’ comments in response to our data sharing statement question. The standard answers are entered here; please edit these to fit your study.

We filled the box and removed the text from the methods section

8. LINE 201: Can get confusing – please change Table 1 to simply ‘performance score’

Agree

9. TABLE 1: Presumably this was an event related to the subsequent pregnancy, so this is unnecessary to say in the Table and patient should be referenced as ‘nonmolar tissue’

This is true, we however are not certain if this is very late complication of the second curettage. Therefore we strongly believe that this should be addressed in the paper. We changed the numbers in the table as suggested and left the marking with the footnote. When the editors think this is not appropriate the footnote can be removed.

The endpoint is the number of chemotherapy cycles: In women needing 2nd line chemotherapy first and second line add to the number. Some of the new headings are therefore no improvements. (See manuscript)

Please let me know if you have any questions. Your prompt response to these queries will be appreciated; please respond no later than COB on **Wednesday, February 6th**.

We wrote the paper in UK English, the wording is a bit mixed in the current version, some UK and some US. I am not aware about the policy of the journal, so I did not change this in the current version

Attached is the manuscript with the changes.

Sincerely,
-Daniel Mosier

Daniel Mosier

Editorial Assistant

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From: [REDACTED]
To: [Stephanie Casway](#)
Subject: RE: O&G Figure Revision: 18-2316
Date: Thursday, January 31, 2019 4:53:48 AM

Dear Ms Casway,

Thank you for the opportunity to check the Figure.

When possible we would like to change the text in the fourth box on the right side: "Allocated to intervention curettage" into "Allocated to intervention second curettage" (this would add the word second)
All numbers have been checked and are correct.

We hope to get a positive reply from the editor soon,

Thank you,

Yours,

Helena van Doorn

Van: Stephanie Casway [SCasway@greenjournal.org]
Verzonden: woensdag 30 januari 2019 18:12
Aan: H.C. van Doorn
Onderwerp: O&G Figure Revision: 18-2316

Good Afternoon Dr. van Doorn,

Your figure has been edited, and a PDF of the figure is attached for your review. Please review the figure CAREFULLY for any mistakes.

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

To avoid a delay, I would be grateful to receive a reply no later than Friday, 2/1. Thank you for your help.

Best wishes,

Stephanie Casway, MA
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