

# 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.*

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

[obgyn@greenjournal.org](mailto:obgyn@greenjournal.org).

**Date:** Jul 13, 2018  
**To:** "Gregory Matthew Gressel" [REDACTED]  
**From:** "The Green Journal" em@greenjournal.org  
**Subject:** Your Submission ONG-18-1119

RE: Manuscript Number ONG-18-1119

Characterization of risk factors and timing of venous thromboembolism in patients with uterine serous carcinoma

Dear Dr. Gressel:

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 Aug 03, 2018, we will assume you wish to withdraw the manuscript from further consideration.

#### REVIEWER COMMENTS:

##### Reviewer #1:

This is a single institution retrospective cohort study to evaluate the risk factors and timing of venous thromboembolism (VTE) for women with uterine serous carcinoma (USC). The authors found that 17% of patients in their cohort had radiologically confirmed VTE. The median time from cancer diagnosis to VTE was 10 months. Risk factors of VTE included HTN, cardiovascular disease, and advanced stage of disease.

Methods: Overall, study design is good.

- Is there a reason why type of surgery was excluded from the analysis? Comparing factors such as MIS vs open procedures, the necessity of radical debulking procedures, and amount of residual disease may affect the risk of perioperative VTE.
- Also, how many of the patients who underwent surgeries were discharged with extended thromboprophylaxis? Although authors comment that median time to VTE is 10 months, it would be interesting to see if those that did have extended prophylactic post-operative anticoagulation had less perioperative VTE in USC patients.

##### Results:

Line 140-141: Authors state that patients who had more than 2 diagnosed major medical co-morbidities had increased risk of VTE ( $p=0.02$ ). Were these co-morbidities inclusive of HTN and cardiovascular disease? It appears that HTN and cardiovascular disease are independent risk factors. Therefore, this statement needs to be clarified.

Line 150-151: Authors state that 36% of patients developed clots while receiving chemotherapy. From Table 2 - 31% developed VTE during adjuvant chemotherapy. If including neoadjuvant chemotherapy, total would be 35%.

Line 160-161: Does median time to clot development include the 36% of patients that developed VTE as the presenting symptom? I think the 36% who presented with VTE is a very important finding, but little emphasis is given to this point.

Table 2 - Did none of the patients have VTE < 6 weeks post-operatively? If so, it would be important to include that in a category illustrating this finding. Also, did they any go home with extended thromboprophylaxis?

##### Reviewer #2:

Thank you for the opportunity to review your article characterization of risk factors and timing of venous thromboembolism in patients with uterine serous carcinoma. This is a retrospective database review with comparison of patients who developed VTE after surgery versus patients who did not. I would like to make some comments regarding the article.

First, and the material and methods, there is no mention of minimally invasive surgery versus open surgery. It may be that all cases were performed via laparotomy, but laparotomy is a significant risk factor for development of venous

thromboembolism. I am sure, also, that open surgery is also correlated with high stage disease, but that should be accounted for in the multivariable analysis.

In the introduction and then again in the results you mention the Khorana scoring system. Either in the text, oriented table, it would be worthwhile to have a summary of the scoring system.

I am also uncertain as to the legitimacy of your conclusion in your abstract that patients with USC would benefit from extended VTE prophylaxis. In your conclusion, you indicate that the majority of the VTEs were diagnosed either preoperatively or long after surgery. How would thromboprophylaxis for 30 or 60 days impact this? I think at best, a retrospective study of this nature, is exploratory in nature and would suggest a larger process effective randomized study is in order.

Last, and I apologize for seeming picky, your references should be edited so that they are uniform in standard for the journal.

Reviewer #3:

This is a nicely written retrospective study with a diverse population that further substantiates the literature that cancer and comorbidities increase the risk of DVT and that risk persists after 6 weeks. This work was NIH sponsored and was presented at the 2018 Society of Gynecologic Oncology meeting.

I think it is important to address the risk of stage for DVT in low risk pathology. In other words, high risk histology has been shown to have an increased risk of DVT as has stage but is it maybe just stage since high risk histology is likely diagnosed at a higher stage? Please discuss.

Similarly, why do you think that lower stages have DVT further out than higher stage? Is it because of the stage or that women with a higher stage are sicker earlier? Again, please include in your discussion.

You need to explain what a Charlson comorbidity index is.

I would eliminate the Kaplan Meier curves on cardiovascular disease and hypertension.

Reviewer #4:

I would be interested to know how many of the patients who developed VTE in the postoperative period received adequate prophylaxis during this time. In the discussion, it is mentioned that not all patients are routinely given VTE prophylaxis. While it has not been shown that extended ppx improves outcomes (as per the discussion section), it might be worth knowing if adequate postop ppx has any effect on outcomes. My guess would be that patients who have not received any prophylaxis would be more likely to eventually develop a VTE, even many weeks out, when compared to patients who were adequately anticoagulated.

I also think it is worth clarifying how many weeks/months postop patients were at the time of VTE. In the discussion, it is stated that the median time to VTE from initial diagnosis is 10 months, but it is not clear to me where these patients were in their postoperative course. Based on Table 2, 60% of patients found to have a VTE were in the postoperative period. I think it's worth exploring how far post-op they were, especially if part of the conclusion is that we should be considering extended anticoagulation for these patients in the postoperative period. This might also help resolve any potential confounding between being post-op and receiving adjuvant chemo given that by definition anyone getting adjuvant chemo is also post-op.

#### STATISTICAL EDITOR COMMENTS:

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

Table 1: The mean values of age or BMI were NS different for VTE vs No VTE, but were the OR for VTE different for older age strata or for obesity classes as defined by BMI?

Table 3, lines 165-167: I assume these were adjusted HRs. If so, should include as footnote the covariates retained in the final model

Figs 1, 2, 3: Need to label the y-axes. Need to include along the x-axis at specified time increments, the number remaining at risk in each cohort.

It would be worthwhile to include the median time (with range or IQR) to VTE for the various risk groups. This would of course exclude those whose presenting symptom was a VTE, so only the remaining 45 women. This could be incorporated into Table 3 or as a separate table. A separate enumeration of risk factors for the 25 women who had VTE as presenting symptom would also be of interest. Also, since the hypothesis generated by these data is that VTE prophylaxis might be warranted and it appears from the figures (since the proportion corresponding to time = 0 is 1.00) that the 25 women who presented with VTE were excluded, need to clearly identify which risk factors were associated with the 25 vs the cohort of 45, since only those would potentially be preventable.

## EDITOR COMMENTS:

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

\*\*\*The notated PDF is uploaded to this submission's record in Editorial Manager. If you cannot locate the file, contact Katie McDermott and she will send it by email – [kmcdermott@greenjournal.org](mailto:kmcdermott@greenjournal.org).\*\*\*

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

1. OPT-IN: Yes, please publish my response letter and subsequent email correspondence related to author queries.
2. OPT-OUT: No, please do not publish my response letter and subsequent email correspondence related to author queries.

3. Based on the forms that have been submitted, Dr. Turker has not met the criteria for authorship. Dr. Turker should be moved to the acknowledgments, or he/she could resubmit a revised author agreement form if he/she filled it out erroneously the first time. All updated and missing forms should be uploaded with the revision in Editorial Manager.

4. Responsible reporting of research studies, which includes a complete, transparent, accurate and timely account of what was done and what was found during a research study, is an integral part of good research and publication practice and not an optional extra. Obstetrics & Gynecology supports initiatives aimed at improving the reporting of health research, and we ask authors to follow specific guidelines for reporting randomized controlled trials (ie, CONSORT), observational studies (ie, STROBE), meta-analyses and systematic reviews of randomized controlled trials (ie, PRISMA), harms in systematic reviews (ie, PRISMA for harms), studies of diagnostic accuracy (ie, STARD), meta-analyses and systematic reviews of observational studies (ie, MOOSE), economic evaluations of health interventions (ie, CHEERS), and quality improvement in health care (ie, SQUIRE 2.0). Include the appropriate checklist for your manuscript type upon submission. Please write or insert the page numbers where each item appears in the margin of the checklist. Further information and links to the checklists are available at <http://ong.editorialmanager.com>. In your cover letter, be sure to indicate that you have followed the CONSORT, MOOSE, PRISMA, PRISMA for harms, STARD, STROBE, CHEERS, or SQUIRE 2.0 guidelines, as appropriate.

5. 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 will be transitioning as much as possible to use of the reVITALize definitions, and we encourage authors to familiarize themselves with them. The obstetric data definitions are available at <http://links.lww.com/AOG/A515>, and the gynecology data definitions are available at <http://links.lww.com/AOG/A935>.

6. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Original Research reports should not exceed 22 typed, double-spaced pages (5,500 words); Case Reports should not exceed 8 typed, double-spaced pages (2,000 words); Review articles should not exceed 25 typed, double-spaced pages (6,250 words); Current Commentary articles should not exceed 12 typed, double-spaced pages (3,000 words); Clinical Practice and Quality articles should not exceed 22 typed, double-spaced pages (5,500 words); Procedures and Instruments articles should not exceed 8 typed, double-spaced pages (2,000 words); Personal Perspectives essays should not exceed 12 typed, double-spaced pages (3,000 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and appendixes).

Please limit your Introduction to 250 words and your Discussion to 750 words.

7. Specific rules govern the use of acknowledgments in the journal. Please edit your acknowledgments or provide more information in accordance with 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 signature on the journal's author agreement 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. Provide a short title of no more than 45 characters (40 characters for case reports), including spaces, for use as a running

foot.

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

In addition, the abstract length should follow journal guidelines. The word limits for different article types are as follows: Original Research articles, 300 words; Reviews, 300 words; Case Reports, 125 words; Current Commentary articles, 250 words; Clinical Practice and Quality, 300 words; Procedures and Instruments, 200 words. Please provide a word count.

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

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

12. Our readers are clinicians and a detailed review of the literature is not necessary. Please shorten the Discussion and focus on how your results affect or change actual patient care. Do not repeat the Results in the Discussion section.

13. Please review the journal's Table Checklist to make sure that your tables conform to journal style. The Table Checklist is available online here: [http://edmgr.ovid.com/ong/accounts/table\\_checklist.pdf](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, that each author has given approval to the final form of the revision, and that the agreement form signed by each author and submitted with the initial version remains valid.

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 Aug 03, 2018, 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

If you would like your personal information to be removed from the database, please contact the publication office.

Nancy C. Chescheir, MD  
Editor-in-Chief  
409 12<sup>th</sup> Street, SW  
Washington, DC 20024  
[obgyn@greenjournal.org](mailto:obgyn@greenjournal.org)

Dear. Dr. Chescheir, the Editorial Board, and expert referees,

Thank you for your careful and thoughtful review of our manuscript “Characterization of risk factors and timing of venous thromboembolism in patients with uterine serous carcinoma.” We would also like to thank you for providing us with a one-week extension on this response as the revised data analysis and reformat of the manuscript took quite some time. After reviewing all of your comments, we noted some common themes that we addressed in the revision.

First, it was apparent that you wanted us to be more granular with timing of VTE in relation to disease status and treatment characteristics. We revisited all 413 charts and collected exact time points for time of presentation to gynecologic oncology or biopsy proved uterine serous cancer (whichever came first), time of surgery until 6 weeks postoperative, start and end of chemotherapy and date of VTE or censorship. We used these time points to generate the risk sets (median time in months to VTE) for each group presented in Table 2. In doing this analysis, a few patients were reclassified as to their treatment status at time of VTE diagnosis, but the overall findings and implications of this paper remain unchanged.

Second, most reviewers commented that they wanted us to clarify surgical risk factors for VTE such as minimally invasive vs. open surgery, presence of residual disease after surgery, and whether or not patients were discharged home with VTE prophylaxis. We also collected these data points which we present in Table 1. Unfortunately, although we have information regarding discharge with VTE prophylaxis after surgery, this practice was not routinely implemented at our institution until after 2013, and many patients in our cohort had surgery before that time. Excluding patients who underwent surgery prior to 2013, who never had surgery, who developed clots prior to surgery, or who were already on anticoagulation for other medical conditions, only 7 patients remained in the analysis. This made it impossible to make any reliable conclusions regarding the association of discharge VTE prophylaxis with postoperative VTE or VTE later in the course of disease. We have mentioned this in our limitations of the study. Please find our responses to each of the individual reviewers’ comments below in red.

REVIEWER COMMENTS:

Reviewer #1:

This is a single institution retrospective cohort study to evaluate the risk factors and timing of venous thromboembolism (VTE) for women with uterine serous carcinoma (USC). The authors found that 17% of patients in their cohort had radiologically confirmed VTE. The median time from cancer diagnosis to VTE was 10 months. Risk factors of VTE included HTN, cardiovascular disease, and advanced stage of disease.

Methods: Overall, study design is good.

- Is there a reason why type of surgery was excluded from the analysis? Comparing factors such as MIS vs open procedures, the necessity of radical debulking procedures, and amount of residual disease may affect the risk of perioperative VTE.

We initially had omitted surgical information from the analysis as many other studies have reported the association of open surgery with VTE compared to minimally invasive surgery and this information was not readily available from our data set. For the 364 patients who underwent surgery, we reviewed their charts for details regarding surgery and found no association between minimally invasive or open surgery or presence of residual disease as presented in Table 1. Although these covariates would not have been selected for inclusion in the multivariate regression model as they were highly non-significant, we included them anyways and they were still not significant adjusting for other covariates. Changes made: lines 134-137, lines 181-182, lines 274-282, Table 1, line 508

- Also, how many of the patients who underwent surgeries were discharged with extended thromboprophylaxis? Although authors comment that median time to VTE is 10 months, it would be interesting to see if those that did have extended prophylactic post-operative anticoagulation had less perioperative VTE in USC patients.

Of the 364 patients who underwent surgery, 46 were discharged home with 28 days of VTE prophylaxis. This practice only became commonplace at our institution after 2013, and we only provide pharmacologic prophylaxis to those patients who undergo open surgery. Excluding patients who underwent surgery prior to 2013, who never had surgery, who developed clots prior to surgery, or who were already on anticoagulation for other medical conditions, only 7 patients remained in the analysis. This made it impossible to make any reliable conclusions regarding the association of discharge VTE prophylaxis with postoperative VTE or VTE later in the course of disease. Larger prospective studies lacking secular trends in administration of VTE prophylaxis are needed to clarify this question as we have mentioned in our discussion. Changes made: lines 188-196, 341-345

Results:

Line 140-141: Authors state that patients who had more than 2 diagnosed major medical co-morbidities had increased risk of VTE ( $p=0.02$ ). Were these co-morbidities inclusive of HTN and cardiovascular disease? It appears that HTN and cardiovascular disease are independent risk factors. Therefore, this statement needs to be clarified.

Medical co-morbidities were examined for their association with VTE both individually and as a composite score of total co-morbid illnesses as presented in Table 1. The composite comorbidity score



included both hypertension as well as cardiovascular disease which were significant as independent risk factors. Covariates included in the regression model were assessed for evidence of collinearity and first order interaction as mentioned in our methods (lines 165-174) and no substantial violations were noted.

Changes made: lines 127-129.

Line 150-151: Authors state that 36% of patients developed clots while receiving chemotherapy. From Table 2 - 31% developed VTE during adjuvant chemotherapy. If including neoadjuvant chemotherapy, total would be 35%.

After reclassification of disease status at time of VTE in revising this manuscript, a total of 22 patients developed VTE during chemo (7 during neoadjuvant chemo and 15 during adjuvant chemo). This accounts for 31% of the 70 patients who developed VTE and this number is reflected in our revision. Changes made: Table 2, line 521.

Line 160-161: Does median time to clot development include the 36% of patients that developed VTE as the presenting symptom? I think the 36% who presented with VTE is a very important finding, but little emphasis is given to this point.

Thank you for bringing this up. After reviewing this comment and those made by other referees, we felt that the term "presenting symptom" was misleading. We intended this term to refer to any patient who was diagnosed with VTE prior to undergoing surgery or chemo, not necessarily that their presenting complaint was leg swelling or shortness of breath leading to diagnosis of VTE and subsequent cancer diagnosis. We have changed the language in the manuscript to reflect this. In our final analysis, 18 patients (21% of the 70 patients with VTE) were diagnosed with VTE between presentation to care or biopsy confirming uterine cancer and initiation of surgery or chemo.

Changes made: Lines 45-47, lines 137-139, lines 199-202 line 283-384, table 2.

Table 2 - Did none of the patients have VTE < 6 weeks post-operatively? If so, it would be important to include that in a category illustrating this finding. Also, did they any go home with extended thromboprophylaxis?

10 participants developed VTE in the 6 weeks following surgery, representing 14% of all participants who developed VTE during follow-up. Median time from surgery to development of VTE in this group was 0.3 months (IQR 0.1, 0.5 months). This data is presented both in the body of the manuscript as well as in Table 2 as a risk set. Please refer to our response to your first comment regarding extended pharmacologic prophylaxis.

Reviewer #2:

Thank you for the opportunity to review<sup>3</sup> your article characterization of risk factors and timing of venous thromboembolism in patients with uterine serous carcinoma. This is a retrospective database review with comparison of patients who developed VT E after surgery versus patients who did not. I would like to make some comments regarding the article.

First, and the material and methods, there is no mention of minimally invasive surgery versus open surgery. It may be that all cases were performed via laparotomy, but laparotomy is a significant risk



factor for development of venous thromboembolism. I am sure, also, that open surgery is also correlated with high stage disease, but that should be accounted for in the multivariable analysis.

Thank you for your review and comments. This point was made by several other reviewers of the paper. Although we found a significant association between VTE diagnosis and advanced stage disease, surgical approach (open vs minimally invasive) was not significant as a covariate either in univariate analysis or multivariable regression. Part of this is probably explained by the fact that many participants in our cohort underwent open surgery for early stage disease before minimally invasive staging surgery for high grade uterine cancer was commonplace at our institution (the followup period ranges from 1999-2016). We have mentioned this in the discussion section.  
Changes made: lines 190-196.

In the introduction and then again in the results you mention the Khorana scoring system. Either in the text, oriented table, it would be worthwhile to have a summary of the scoring system.

We have explained the Khorana scoring system further within the body of the manuscript including purpose, components of the scoring system and risk stratification categories. We have also referenced the primary citation for the original publication by Dr. Khorana in *Blood*.  
Changes made: Lines 293-331.

I am also uncertain as to the legitimacy of your conclusion in your abstract that patients with USC would benefit from extended VTE prophylaxis. In your conclusion, you indicate that the majority of the VTEs were diagnosed either preoperatively or long after surgery. How would thromboprophylaxis for 30 or 60 days impact this? I think at best, a retrospective study of this nature, is exploratory in nature and would suggest a larger process effective randomized study is in order.

Thank you and we completely agree. This is a retrospective cohort study and we cannot make any causal inferences or conclude definitively that patients would benefit from thromboprophylaxis longer than 30 or 60 days. However, our study does demonstrate that many patients develop VTE at other time points in their disease course including prior to initiation of treatment (surgery or chemo) and during neo-adjuvant or adjuvant chemotherapy. We believe that at the least, this study generates the hypothesis that a prospective randomized study examining prophylactic anticoagulation in patients undergoing adjuvant therapy would be helpful. We are very transparent about this in our discussion and conclusions.  
Changes made: lines 343-384.

Last, and I apologize for seeming picky, your references should be edited so that they are uniform in standard for the journal.

This is not picky at all! We have formatted our references according to your document "Obstetrics & Gynecology: *Reference Style*" using Mendeley reference management software with *Obstetrics & Gynecology* reference format. Please let us know if you require additional revisions to this list.

Reviewer #3:

This is a nicely written retrospective study with a diverse population that further substantiates the literature that cancer and comorbidities increase the risk of DVT and that risk persists after 6

weeks. This work was NIH sponsored and was presented at the 2018 Society of Gynecologic Oncology meeting.

I think it is important to address the risk of stage for DVT in low risk pathology. In other words, high risk histology has been shown to have an increased risk of DVT as has stage but is it maybe just stage since high risk histology is likely diagnosed at a higher stage? Please discuss.

This study examines only patients with high risk histology (uterine serous carcinoma) and does not include any patients with low risk pathology (endometrioid carcinoma). Therefore we are not able to comment the risk of stage for DVT in low risk pathology. We can however conclude from this study that advanced stage disease in this cohort is highly associated with risk of DVT because all participants had the same histologic subtype of cancer.

Similarly, why do you think that lower stages have DVT further out than higher stage? Is it because of the stage or that women with a higher stage are sicker earlier? Again, please include in your discussion.

Venous thromboembolism in cancer results from venous stasis (immobility), hypercoagulability (cancer) and endothelial dysfunction (vascular injury). The fact that we identified no significant association between surgical approach (minimally invasive vs open) and time to VTE suggests that immobility and surgical insult have less of a significant impact on thrombogenesis in this population. The fact that advanced stage cancer is so significantly associated with VTE diagnosis suggests that potentially it's the burden of disease itself and the inflammatory markers and coagulative factors secreted by the tumor volume that results in earlier thrombosis. We have no serum studies to examine this hypothesis. We have discussed this more thoroughly in our manuscript.  
Changes made: Lines 279-282

You need to explain what a Charlson comorbidity index is.

Thank you for pointing this out. This was a typographic error. We did not use the Charlson Comorbidity index in our analysis, but rather a composite score of number of medical comorbidities as explained in table 1. We have corrected this in the paper.  
Changes made: Line 273.

I would eliminate the Kaplan Meier curves on cardiovascular disease and hypertension.

We have eliminated these figures based on your recommendation.

Reviewer #4:

I would be interested to know how many of the patients who developed VTE in the postoperative period received adequate prophylaxis during this time. In the discussion, it is mentioned that not all patients are routinely given VTE prophylaxis. While it has not been shown that extended ppx improves outcomes (as per the discussion section), it might be worth knowing if adequate postop ppx has any effect on outcomes. My guess would be that patients who have not received any prophylaxis would be

more likely to eventually develop a VTE, even many weeks out, when compared to patients who were adequately anticoagulated.

Of the 364 patients who underwent surgery, 46 were discharged home with 28 days of VTE prophylaxis. This practice only became commonplace at our institution after 2013, and we only provide pharmacologic prophylaxis to those patients who undergo open surgery. Excluding patients who underwent surgery prior to 2013, who never had surgery, who developed clots prior to surgery, or who were already on anticoagulation for other medical conditions, only 7 patients remained in the analysis. This made it impossible to make any reliable conclusions regarding the association of discharge VTE prophylaxis with postoperative VTE or VTE later in the course of disease. Larger prospective studies lacking secular trends in administration of VTE prophylaxis are needed to clarify this question as we have mentioned in our discussion.

Changes made: lines 188-196, 341-345

I also think it is worth clarifying how many weeks/months postop patients were at the time of VTE. In the discussion, it is stated that the median time to VTE from initial diagnosis is 10 months, but it is not clear to me where these patients were in their postoperative course. Based on Table 2, 60% of patients found to have a VTE were in the postoperative period. I think it's worth exploring how far post-op they were, especially if part of the conclusion is that we should be considering extended anticoagulation for these patients in the postoperative period. This might also help resolve any potential confounding between being post-op and receiving adjuvant chemo given that by definition anyone getting adjuvant chemo is also post-op.

This was an excellent suggestion. The statistical editor also made the suggestion that time to VTE in individual risk sets should be clarified. We have thoroughly explored this in Table 2. Patients who developed VTE in the 6 week postoperative period had a median time from presentation/diagnosis to VTE of 1.4 months and from surgery to VTE of 0.3 months. However, those who developed VTE during adjuvant chemotherapy had a median time from presentation/ diagnosis to VTE of 13.7 months and from surgery to VTE of 13.2 months. This suggests that the risk of VTE extends well beyond the postoperative period.

Changes made: Table 2, line 521.

#### STATISTICAL EDITOR COMMENTS:

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

Table 1: The mean values of age or BMI were NS different for VTE vs No VTE, but were the OR for VTE different for older age strata or for obesity classes as defined by BMI?

We examined these continuous variables in many different forms and found no association. Examining age in different quantiles or by age  $\geq 80$  years old demonstrated no association. Likewise, looking at BMI in groups (BMI  $<29.9$ ,  $30.0-34.9$ ,  $35-39.9$ ,  $>40.0$ ) demonstrated no significant differences.

Table 3, lines 165-167: I assume these were adjusted HRs. If so, should include as footnote the covariates retained in the final model

You are correct. These are adjusted hazard ratios and the covariates listed in Table 3 are the covariates retained in the final model. We have added a footnote to this table to that effect. Changes made: Table 3, lines 536-537

Figs 1, 2, 3: Need to label the y-axes. Need to include along the x-axis at specified time increments, the number remaining at risk in each cohort.

Based on Reviewer #4's comments, we have eliminated figures 2 and 3 and have altered Figure 1 as you requested.

It would be worthwhile to include the median time (with range or IQR) to VTE for the various risk groups. This would of course exclude those whose presenting symptom was a VTE, so only the remaining 45 women. This could be incorporated into Table 3 or as a separate table. A separate enumeration of risk factors for the 25 women who had VTE as presenting symptom would also be of interest. Also, since the hypothesis generated by these data is that VTE prophylaxis might be warranted and it appears from the figures (since the proportion corresponding to time = 0 is 1.00) that the 25 women who presented with VTE were excluded, need to clearly identify which risk factors were associated with the 25 vs the cohort of 45, since only those would potentially be preventable.

This was an excellent suggestion. We have included median time (IQR) to VTE for all at-risk groups within the cohort. You can find this information in Table 2.

#### EDITOR COMMENTS:

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

\*\*\*The notated PDF is uploaded to this submission's record in Editorial Manager. If you cannot locate the file, contact Katie McDermott and she will send it by email – [kmcdermott@greenjournal.org](mailto:kmcdermott@greenjournal.org).\*\*\*

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

1. OPT-IN: Yes, please publish my response letter and subsequent email correspondence related to author queries.
2. OPT-OUT: No, please do not publish my response letter and subsequent email correspondence related to author queries.

We would like to OPT-IN (Yes, please publish my response letter and subsequent email correspondence related to author queries).

3. Based on the forms that have been submitted, Dr. Turker has not met the criteria for authorship. Dr. Turker should be moved to the acknowledgments, or he/she could resubmit a revised author agreement form if he/she filled it out erroneously the first time. All updated and missing forms should be uploaded with the revision in Editorial Manager.

This was an oversight on our part. Dr. Turker meets the criteria for authorship and we have uploaded her revised form to the Editorial Manager.

4. Responsible reporting of research studies, which includes a complete, transparent, accurate and timely account of what was done and what was found during a research study, is an integral part of good research and publication practice and not an optional extra. Obstetrics & Gynecology supports initiatives aimed at improving the reporting of health research, and we ask authors to follow specific guidelines for reporting randomized controlled trials (ie, CONSORT), observational studies (ie, STROBE), meta-analyses and systematic reviews of randomized controlled trials (ie, PRISMA), harms in systematic reviews (ie, PRISMA for harms), studies of diagnostic accuracy (ie, STARD), meta-analyses and systematic reviews of observational studies (ie, MOOSE), economic evaluations of health interventions (ie, CHEERS), and quality improvement in health care (ie, SQUIRE 2.0). Include the appropriate checklist for your manuscript type upon submission. Please write or insert the page numbers where each item appears in the margin of the checklist. Further information and links to the checklists are available at <http://onq.editorialmanager.com>. In your cover letter, be sure to indicate that you have followed the CONSORT, MOOSE, PRISMA, PRISMA for harms, STARD, STROBE, CHEERS, or SQUIRE 2.0 guidelines, as appropriate.

We have completed the STROBE checklist for cohort studies as this is a retrospective cohort and included it with our resubmission. We have also indicated use of these guidelines in our cover letter as well as in the methods section of our manuscript.

5. 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 will be transitioning as much as possible to use of the reVITALize definitions, and we encourage authors to familiarize themselves with them. The obstetric data definitions are available at <http://links.lww.com/AOG/A515>, and the gynecology data definitions are available at <http://links.lww.com/AOG/A935>.

We have reviewed these definitions and they do not apply to our study.

6. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Original Research reports should not exceed 22 typed, double-spaced pages (5,500 words); Case Reports should not exceed 8 typed, double-spaced pages (2,000 words); Review articles should not exceed 25 typed, double-spaced pages (6,250 words); Current Commentary articles should not exceed 12 typed, double-spaced pages (3,000 words); Clinical Practice and Quality articles should not exceed 22 typed, double-spaced pages (5,500 words); Procedures and Instruments articles should not exceed 8 typed, double-spaced pages (2,000 words); Personal Perspectives essays should not exceed 12 typed, double-spaced pages (3,000 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and appendixes).

Please limit your Introduction to 250 words and your Discussion to 750 words.

Our manuscript meets your requirements for "Original Research Reports"- it is 2261 words and 22 typed, double spaced pages. Our introduction is now 249 words and our discussion is 720 words.

7. Specific rules govern the use of acknowledgments in the journal. Please edit your acknowledgments or provide more information in accordance with 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 signature on the journal's author agreement 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).

We have edited our acknowledgements as requested.

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

We have already included this. Your requirements regarding abbreviations allow for abbreviations in the running foot which we have included. Please let us know if you wish us to changes the short title.

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

We have complied with these requirements

In addition, the abstract length should follow journal guidelines. The word limits for different article types are as follows: Original Research articles, 300 words; Reviews, 300 words; Case Reports, 125 words; Current Commentary articles, 250 words; Clinical Practice and Quality, 300 words; Procedures and Instruments, 200 words. Please provide a word count.

The abstract word count for our manuscript is 267 words which meets the guidelines for Original Research Articles

10. Only standard abbreviations and acronyms are allowed. A selected list is available online

at <http://edmgr.ovid.com/ong/accounts/abbreviations.pdf>. Abbreviations and acronyms cannot be used in the title or précis. Abbreviations and acronyms must be spelled out the first time they are used in the abstract and again in the body of the manuscript.

Although the abbreviation for venous thromboembolism (VTE) is not listed in the approved list of abbreviations, we have met the other stipulations laid forth for abbreviations. VTE is a commonly used abbreviation in the literature, including multiple recent articles in *Obstetrics & Gynecology* as well as ACOG practice guidelines. We feel it would be onerous for your readers to see "venous thromboembolism" spelled out over 60 times and we are hoping that you would consider accepting the use of this abbreviation in our manuscript.

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

We have corrected this as requested

12. Our readers are clinicians and a detailed review of the literature is not necessary. Please shorten the Discussion and focus on how your results affect or change actual patient care. Do not repeat the Results in the Discussion section.

We have removed significant portions of the literature review in our discussion and have avoided repeating results.

13. Please review the journal's Table Checklist to make sure that your tables conform to journal style. The Table Checklist is available online here: [http://edmgr.ovid.com/ong/accounts/table\\_checklist.pdf](http://edmgr.ovid.com/ong/accounts/table_checklist.pdf).

We have reviewed this checklist and have eliminated any inconsistencies.



**From:** [REDACTED]  
**To:** [Rebecca Benner](#)  
**Cc:** [Denise Shields](#); [Stephanie Casway](#)  
**Subject:** Re: Author Queries: 18-1119R1  
**Date:** Tuesday, August 14, 2018 7:45:38 PM  
**Attachments:** [REDACTED]

---

Dear Dr Chescheir and Ms. Benner,

Please see below a point-by-point list of our responses as well the attached tracked manuscript. Thank you for your thoughtful review and continued help with this submission.

Best regards,

Greg Gressel

1. Page 4:

1. The objective for the abstract should be a simple "to" statement without background.

We have changed the objective as requested.

2. In the abstract, please provide absolute numbers as well as whichever effect size you are reporting + Confidence intervals. P values may be omitted for space concerns. By absolute values, I mean something like: xx (outcome in exposed)/yy(outcome in unexposed) (zz%) (Effect size= ; 95% CI= ). An example might be: Outcome 1 was more common in the exposed than the unexposed 60%/20% (Effect size=3;95% CI 2.6-3.4)

We have made these changes as requested.

3. Page 10 (line 174) has 86%. Which percentage is correct?

84% is the correct number (59 of 70 patients with VTE) excluding the one patient for whom there was inadequate clinical data to characterize timing associated with VTE. Thank you for picking this up. We have corrected this in the body of the manuscript as well.

2. Page 5:

1. What in the abstract would support a recommendation to offer VTE prophylaxis to

women with this disorder only during chemotherapy? What about to women w/ stage 4 disease, for instance? What about post operatively?

We agree with this observation. Risk of VTE in our study was very high at all time points during the continuum of treatment for uterine serous carcinoma, including prior to surgery, during neoadjuvant chemotherapy, during adjuvant chemotherapy and after completion of treatment. Because our study also demonstrated that the Khorana score would not have appropriately risk stratified patients undergoing chemotherapy, we decided to focus on this time point specifically given space limitations. But we have taken your suggestion and revised the abstract to state that VTE prophylaxis may be beneficial in patients with uterine serous carcinoma during other time points along the continuum of disease rather than only in the postoperative period, especially for those with advanced cancer.

3. Page 6:

1. Was this for a specific cancer or any cancer? Any gyn cancer? Important distinctions as it seems that it varies by type of cancer in some reports.

The study that was cited is the largest cohort in the literature examining incidence and predictors of VTE in ambulatory chemotherapy patients and specifically looked at patients with colorectal, lung, ovarian, pancreatic and gastric malignancies. We specified this cancer sites within the manuscript. Given that they did not examine endometrial malignancies, we feel the findings of this study are even more important.

2. Please clarify your primary and secondary outcomes.

The primary outcome of the study was time from presentation to radiologic diagnosis of VTE. Secondary outcomes included time from surgical staging to VTE and time from initiation of chemotherapy to VTE. We have clarified this in the manuscript.

4. Page 7:

1. Please include the name of the institution that provided the IRB approval.

We have included this information

5. Page 8:

1. Is one of your secondary objectives to evaluate the usefulness of the Khorana scoring

system in this population?

Yes we have clarified this in our list of study objectives (page 5, line 109)

6. Page 9:

1. For data presented in the text, please provide the raw numbers as well as data such as percentages, effect size (OR, RR, etc) as appropriate and 95% CI's.

We have included the raw numbers as requested

2. Please clarify what you mean by “during follow up”. Your study by your description says “Timing of VTE was calculated as the number of months elapsed from date of presentation to care with a gynecologic oncologist or biopsy confirmed uterine cancer (whichever came first) until date of VTE diagnosis.” Is follow up based on this initiation of time for calculating time of VTE? I believe that is what you mean, but clinical “Follow up” typically means “after treatment”.

This is an extremely important point and we apologize for the omission. Any survival analysis requires a definition of “failure” (in this case VTE), or “censorship” (usually date of last followup or end of the study period). Upon reading our methods, we realize that we neglected to include definition of how we censored patients. We have rectified this (lines 141-143). Our use of the term “follow-up” in the manuscript was inconsistent as you pointed out. We have changed the expression “during follow-up” in line 176 to “during the study period.”

7. Page 10:

1. Again—follow up question

Our use of the term “follow-up time” here is more accurate and we have clarified that we mean “from presentation to VTE or censorship”.

2. The abstract has 84%. Which percentage is correct?

84% is correct. We have changed this.

8. Page 12:

1. This is causal language; in this study, you can only report associations.

We agree. One of the reviewers had asked us to conjecture why DVT occurs earlier in those with advanced disease than those with early stage cancer and this was our attempt to make sense of the data. After reviewing your comment, we have decided to eliminate these hypotheses.

2. Does this include neo-adjuvant chemo?

It does. We have clarified this in lines 259-260.

9. Page 14:

1. We discourage claims of first reports since they are often difficult to prove. How do you know this is the first report? If this is based on a systematic search of the literature, that search should be described in the text (search engine, search terms, date range of search, and languages encompassed by the search). If on the other hand, it is not based on a systematic search but only on your level of awareness, it is not a claim we permit.

We have removed this entire section from the manuscript.

When we sent the revision letter, there was a link in EM to a PDF of your original submission that contained three editor queries. We did not see a response to those queries in your point-by-point response, so they are outlined below. I have also attached the PDF for your reference. Please respond to these questions in your emailed response:

1. Page 14: Please look at the Instructions for authors for section header instructions. *This is resolved—staff editor changed this heading to “Discussion” (see Word file).*

Thank you and we apologize for having neglected these comments before.

2. Page 14: This statement should be with the reporting below of the retrospective Khorana score.

After the extensive revisions we made to our discussion section, this statement no longer exists and all discussion of the Khorana score has been relocated to one section (lines 269-

3. Page 17: As one considers the biologic plausibility of use of VTE prophylaxis to completion of therapy say, what would be the explanation for why these women get clots so late? Is it hypercoagulability related to persistent cancer? Could it be some direct effect on the endothelium by chemotherapy (perhaps w with underlying cancer risk factor, previous surgery, and hypertension all being risk factors?) Women with this disease tend to be heavy-- post op and with the chemo regimen used, is there more risk for venous stasis due to decreased activity? Just running through Virchow's triad to find an explanation that might inform a trial.

Yes, we have also been thinking of how to make sense of all of this. Our study demonstrated that risk of thrombosis increases as stage of disease increases from stage I to stage IV and that clots present sooner at more advanced stages. We feel this reflects the "hypercoagulability" monad of Virchow's triad. Perhaps the disease itself produces inflammatory cytokines resulting in hypercoagulability that increases with the burden of disease. Perhaps tumor lysis during chemotherapy or the thrombogenic nature of chemo itself contributes to this. The fact that we found no association between invasiveness of surgical approach suggests that vascular injury/ endothelial dysfunction probably plays less of a role. We also found no association between diagnosis of obesity (or BMI as a continuous variable) with VTE, which suggests to us that venous stasis also probably plays less of a role. But again this is all conjecture. It would be infeasible (especially based on observational data) to place women diagnosed with uterine serous carcinoma on VTE prophylaxis for the rest of their lives. Perhaps an ideal place to start would be to perform a study randomizing woman undergoing adjuvant chemotherapy for uterine serous cancer, to pharmacologic prophylaxis versus placebo only during their adjuvant treatment. If a significant reduction in VTE events were noted (or if VTE events continued even after completing chemotherapy), it would have important impact on clinical care.

For the purposes of this manuscript, we have avoided making these conjectures and mentioned in lines 294-297 that due to the observational nature of the study, we are unable to make any definitive conclusions regarding causal association of Virchow's triad and VTE in our cohort.

Gregory M. Gressel MD, FACOG  
Assistant Professor  
Department of Obstetrics, Gynecology & Women's Health  
Division of Gynecologic Oncology  
Albert Einstein College of Medicine  
Montefiore Medical Center  
[REDACTED]

---

**From:** Rebecca Benner <RBenner@greenjournal.org>

**Sent:** Tuesday, August 14, 2018 2:01:53 PM

**To:** [REDACTED]

**Cc:** Denise Shields; Stephanie Casway

**Subject:** Author Queries: 18-1119R1

*CAUTION: This email comes from an external source; the attachments and/or links may compromise our secure environment. Do not open or click on suspicious emails. Please click on the "Phish Alert" button on the top right of the Outlook dashboard to report any suspicious emails.*

Dear Dr. Gressel,

Thank you for submitting your revised manuscript. It has been reviewed by the Editor, and there are a few issues that must be addressed before we can consider your manuscript further.

First, however, a note from Dr. Chescheir—Thank you very much for submitting your revision and for doing the re-analyses as you did. I realize that to get that data there was a lot of recovery of data from charts to do. This has made it a stronger paper.

Attached you will find a Word file of the revised article with our comments, which are also outlined below:

1. Page 4:
  - a. The objective for the abstract should be a simple "to" statement without background.
  - b. In the abstract, please provide absolute numbers as well as whichever effect size you are reporting + Confidence intervals. P values may be omitted for space concerns. By absolute values, I mean something like: xx (outcome in exposed)/yy(outcome in unexposed) (zz%) (Effect size= ; 95% CI= ). An example might be: Outcome 1 was more common in the exposed than the unexposed 60%/20% (Effect size=3;95% CI 2.6-3.4)
  - c. Page 10 (line 174) has 86%. Which percentage is correct?
2. Page 5:

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  - a. Was this for a specific cancer or any cancer? Any gyn cancer? Important distinctions as it seems that it varies by type of cancer in some reports.
  - b. Please clarify your primary and secondary outcomes.
4. Page 7:
  - a. Please include the name of the institution that provided the IRB approval.
5. Page 8:
  - a. Is one of your secondary objectives to evaluate the usefulness of the Khorana scoring system in this population?
6. Page 9:
  - a. For data presented in the text, please provide the raw numbers as well as data such as percentages, effect size (OR, RR, etc) as appropriate and 95% CI's.
  - b. Please clarify what you mean by "during follow up". Your study by your description says "Timing of VTE was calculated as the number of months elapsed from date of presentation to care with a gynecologic oncologist or biopsy confirmed uterine cancer (whichever came first) until date of VTE diagnosis." Is follow up based on this initiation of time for calculating time of VTE? I believe that is what you mean, but clinical "Follow up" typically means "after treatment".
7. Page 10:
  - a. Again—follow up question
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8. Page 12:
  - a. This is causal language; in this study, you can only report associations.
  - b. Does this include neo-adjuvant chemo?
9. Page 14:
  - a. We discourage claims of first reports since they are often difficult to prove. How do you know this is the first report? If this is based on a systematic search of the literature, that search should be described in the text (search engine, search terms, date range of search, and languages encompassed by the search). If on the other hand, it is not based on a systematic search but only on your level of awareness, it is not a claim we permit.

When we sent the revision letter, there was a link in EM to a PDF of your original submission that contained three editor queries. We did not see a response to those queries in your point-by-point response, so they are outlined below. I have also attached the PDF for your reference. Please respond to these questions in your emailed response:



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3. Page 17: As one considers the biologic plausibility of use of VTE prophylaxis to completion of therapy say, what would be the explanation for why these women get clots so late? Is it hypercoagulability related to persistent cancer? Could it be some direct effect on the endothelium by chemotherapy (perhaps w with underlying cancer risk factor, previous surgery, and hypertension all being risk factors?) Women with this disease tend to be heavy--post op and with the chemo regimen used, is there more risk for venous stasis due to decreased activity? Just running through Virchow's triad to find an explanation that might inform a trial.

Please respond point-by-point to these queries in a return email, and make the requested changes to the manuscript. When revising, please leave the track changes on, and do not use the “Accept all Changes” function in Microsoft Word.

Please let me know if you have any questions. Your prompt response to these queries will be appreciated; please respond by noon on **August 17, 2018**.

Sincerely,  
Rebecca Benner

--

Rebecca S. Benner, MPS  
Senior Director and Managing Editor  
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**From:** [REDACTED]  
**To:** [Stephanie Casway](#)  
**Subject:** Re: O&G Figure Revision: 18-1119  
**Date:** Tuesday, August 21, 2018 9:40:27 AM

---

Hello Stephanie,

This looks great! Thank you for all of your hard work on the figure. We have no further edits.

Best regards,

Greg Gressel

On Tue, Aug 21, 2018 at 8:34 AM, Stephanie Casway <[SCasway@greenjournal.org](mailto:SCasway@greenjournal.org)> wrote:

Good Morning Dr. Gressel,

Your figure has been edited, and PDFs of the figure and legend are attached for your review. Please review the figure and legend 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 Thursday, 8/23. Thank you for your help.

Best wishes,

Stephanie Casway, MA  
Production Editor

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|

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Gregory M. Gressel MD

[REDACTED]