

# OBSTETRICS & GYNECOLOGY



**NOTICE:** This document contains correspondence generated during peer review and subsequent revisions but before transmittal to production for composition and copyediting:

- Comments from the reviewers and editors (email to author requesting revisions)
- Response from the author (cover letter submitted with revised manuscript)\*

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

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

Questions about these materials may be directed to the *Obstetrics & Gynecology* editorial office:  
[obgyn@greenjournal.org](mailto:obgyn@greenjournal.org).

**Date:** Jul 24, 2019  
**To:** "Richard Michael Burwick" [REDACTED]  
**From:** "The Green Journal" em@greenjournal.org  
**Subject:** Your Submission ONG-19-991

RE: Manuscript Number ONG-19-991

Pregnancy-Associated Atypical Hemolytic Uremic Syndrome: A Systematic Review of Case Reports

Dear Dr. Burwick:

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 08, 2019, we will assume you wish to withdraw the manuscript from further consideration.

#### REVIEWER COMMENTS:

Reviewer #1: This is a systematic review that sought to evaluate the presentation, diagnosis, treatment and outcomes of gravid patients with atypical hemolytic uremic syndrome (p-aHUS), before and after eculizumab became available. After executing their search algorithm and reviewing the articles for inclusion, 48 case reports describing 60 unique cases of p-aHUS with a total of 66 total pregnancies. Twelve of these cases were patients with previous diagnosis of HUS and 54 were first episode cases. Most of the cases of first episode HUS were postpartum, and associated with many poor obstetrical outcomes, nearly the cases of known HUS preceding pregnancy had very poor outcomes. Eculizumab was associated with higher rates of disease remission after it became available. The authors conclude that p-aHUS usually presents in the postpartum period often following obstetrical complication and eculizumab is most effective for achieving disease remission. Ways in which this manuscript could be improved include:

Lines 202-203: What were the actual numbers of each of these obstetrical outcomes? I would enumerate here.

Line 253: How easy is it to obtain complement genetic testing? What labs offer it? Again as a clinician, what do I need to know to order this lab?

Line 256: How widely available and costly is eculizumab? Were most of the cases managed with a multi-disciplinary team? What does the practicing obstetrician need to know about starting and managing this drug?

Reviewer #2: Gupta and colleagues submit a systematic review from published case reports to "evaluate disease presentation, diagnosis, treatment, and clinical outcomes in women with pregnancy-associated atypical hemolytic uremic syndrome (p-aHUS), before and after eculizumab". This Reviewer would request the Authors to address the following:

Line 27...In the Precis, Abstract and elsewhere in the manuscript, the Authors make the statement "eculizumab is most effective for achieving disease remission" in comparison to other treatment modalities. With this retrospective study design originating from published case reports, such a strong conclusion cannot be made, as timing, sequence and duration of treatment modalities cannot be compared. Their strong claim of eculizumab as the "most effective" of treatments should be toned-down.

Line 60...The Authors describe atypical HUS; a brief differentiation from typical HUS would be of interest to the obstetrical Reader.

Line 113...Are there any other monoclonal antibodies besides eculizumab used for p-aHUS?

Line 154...What date defines "the era after eculizumab"? A PubMed search shows the first publication with eculizumab was in 2002.

Line 169...The acronym (TMA) for the term "thrombotic microangiopathy" should be spelled out at first use.

Line 229...What sequence of treatment do the Authors recommend for the diagnosis of p-aHUS during pregnancy or the postpartum period?

Table 1...The Authors report a demographic variable of "Primip", which this Reviewer interprets as women who delivered their first child as a result of the index pregnancy. However these women would be nulliparous (i.e. Nullip) at the time of p-aHUS diagnosis if they had not yet delivered. Thus this term may be confusing to the Reader... (i.e. a primiparous woman has given birth to 1 child). Are they referring to the parity status after delivery in index cases? It may be better to report gravidity and or parity, in relationship to pre-delivery in each index pregnancy.

Thank you very much for requesting my review of this interesting manuscript.

Reviewer #3: The authors performed a systematic review of pregnancy-associated atypical hemolytic uremic syndrome (p-aHUS) case reports, to evaluate disease presentation, diagnosis, treatment, and clinical outcomes, before and after eculizumab.

The manuscript is well written and addresses a topic important to patients and multidisciplinary team of clinicians (e.g., Maternal-Fetal Medicine, Nephrology, Hematology, Critical Care).

What is already reviewed and available?

1. NEJM 2013 (reference 20) - A study that changed clinical practice
  - \* Eculizumab inhibited complement-mediated thrombotic microangiopathy and was associated with significant time-dependent improvement in renal function in patients with atypical hemolytic-uremic syndrome.
  - \* Eculizumab was associated with a significant improvement in health-related quality of life.
2. An excellent review and take-home message (reference 17), and case report (reference 68) by the authors;
3. Reports in Obstet Gynecol (references 23 and 60);
4. Others Reports in Hematology (reference 27) and Nephrology (reference 24)

What does this study added?

Discussion

Page 14 lines 272-276. Agreed

#### STATISTICAL EDITOR COMMENTS:

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

Tables 1, 2: These Tables could be placed in supplemental on-line material with a concise summary in main text. Need units for age.

Table 3, 4: Since the two cohorts had N = 37 and N = 17, the precision cited for all %s should be rounded to nearest integer, not to 0.1% precision. Need units for maternal age, gestational age.

lines 126-127, Tables 3,4: Many of the comparisons involve 2x2 tables with some entries < 5. Those should have been tested with Fisher's test, not Chi-square. This will change the p-values of many entries. Should also specify what "non-parametric test of medians" was used.

The comments re: prognosis may be influenced by selection bias, since these were all case reports that had been published and may not be a representative sample.

## EDITOR COMMENTS:

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

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

- please add the Alexion Pharmaceuticals is the manufacturer of eculizumab.
- in methods, please define atypical (as compared to typical) HUS
- did you look for more rigorous types of studies, such as RCT's, retrospective cohort studies, etc? Would seem a shame to not have included these a limited to only case reports.
- Why would you include these 12 cases if you study is about atypical Pregnancy associated HUS?
- Differentiate from HUS
- please explain ADAMTS13 diagnostic role
- Move this sentence to precede second sentence in this paragraph.
- Since these labs are not obtained routinely, could you tell us the presenting symptoms or findings that prompted the laboratory testing?
- Don't describe this as different eras. Prior to introduction of the drug and after, or pre and post 2011 are ok. Same is true throughout the manuscript. I Also, this implies that after 2011, eculizumab was always used. Is that true? You seem to be implying that women had different disease severity prior to vs after 2011. Why would you think so? Same question as it relates to sentence starting on line 161. I'm just not getting where you are going with this information couched this way.
- do you mean "prior to 2011"?
- as you are writing this, it seems that its the drug that was the driver behind the change in diagnostic testing. Wasn't it really the development and refinement of ADAMTS13 testing, independent of the drug. And again, "before and after eculizumab" is engrandizing the introduction of this drug. Could you please provide the dates for the introduction and widespread uptake of ADAMTS13 testing as that seems way more relevant.
- what group makes up the "21" here.
- when was the diagnosis made? What I'm getting at, was the drug withheld until after delivery?
- Please edit. As written, it reads that these 15 women reported the use of the standard dose. Perhaps, Of the 15 women treated....., the standard loading regimen was used in 12 (80%).....
- specify that this data is from non pregnant people.
- Please temper this statement. While you data is compelling, this is all based on case reports which may result in a high degree of bias in the data. Here, and in each instance such as the precis and abstract, as well as the text, you need to avoid describing it as "most effective".

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

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

3. As of December 17, 2018, Obstetrics & Gynecology has implemented an "electronic Copyright Transfer Agreement" (eCTA) and will no longer be collecting author agreement forms. When you are ready to revise your manuscript, you will

be prompted in Editorial Manager (EM) to click on "Revise Submission." Doing so will launch the resubmission process, and you will be walked through the various questions that comprise the eCTA. Each of your coauthors will receive an email from the system requesting that they review and electronically sign the eCTA.

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

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

\*The manuscript's guarantor.

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

5. Obstetrics & Gynecology follows the Good Publication Practice (GPP3)\* guideline for manuscripts that report results that are supported or sponsored by pharmaceutical, medical device, diagnostics and biotechnology companies. The GPP3 is designed to help individuals and organization maintain ethical and transparent publication practices.

(1) Adherence to the GPP3 guideline should be noted in the cover letter.

(2) For publication purposes, the portions of particular importance to industry-sponsored research are below. In your cover letter, please indicate whether the following statements are true or false, and provide an explanation if necessary:

(2a) All authors had access to relevant aggregated study data and other information (for example, the study protocol) required to understand and report research findings.

(2b) All authors take responsibility for the way in which research findings are presented and published, were fully involved at all stages of publication and presentation development and are willing to take public responsibility for all aspects of the work.

(2c) The author list accurately reflects all substantial intellectual contributions to the research, data analyses, and publication or presentation development. Relevant contributions from persons who did not qualify as authors are disclosed in the acknowledgments.

(2d) The role of the sponsor in the design, execution, analysis, reporting, and funding (if applicable) of the research has been fully disclosed in all publications and presentations of the findings. Any involvement by persons or organizations with an interest (financial or nonfinancial) in the findings has also been disclosed.

(2e) All authors have disclosed any relationships or potential competing interests relating to the research and its publication or presentation.

(3) The abstract should contain an additional heading, "Funding Source," and should provide an abbreviated listing of the funder(s).

(4) In the manuscript, a new heading—"Role of the Funding Source"—should be inserted before the Methods and contain a detailed description of the sponsor's role as well as the following language:

"The authors had access to relevant aggregated study data and other information (such as study protocol, analytic plan and report, validated data table, and clinical study report) required to understand and report research findings. The authors take responsibility for the presentation and publication of the research findings, have been fully involved at all stages of publication and presentation development, and are willing to take public responsibility for all aspects of the work. All individuals included as authors and contributors who made substantial intellectual contributions to the research, data analysis, and publication or presentation development are listed appropriately. The role of the sponsor in the design, execution, analysis, reporting, and funding is fully disclosed. The authors' personal interests, financial or non-financial, relating to this research and its publication have been disclosed." Authors should only include the above statement if all of it is true, and they should attest to this in the cover letter (see #2, above).

\*From Battisti WP, Wager E, Baltzer L, Bridges D, Cairns A, Carswell CI, et al. Good publication practice for communicating company-sponsored medical research: GPP3. *Ann Intern Med* 2015;163:461-4.

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

7. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Review articles should not exceed 25 typed, double-spaced pages (6,250 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, tables, boxes, figure legends, and print appendixes) but exclude references.

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

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

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

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

11. Line 225: We discourage claims of first reports since they are often difficult to prove. How do you know this is the first report? If this is based on a systematic search of the literature, that search should be described in the text (search engine, search terms, date range of search, and languages encompassed by the search). If on the other hand, it is not based on a systematic search but only on your level of awareness, it is not a claim we permit.

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

13. Figure 1 may be resubmitted as-is.

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

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

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

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

Again, your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Aug 08, 2019, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Nancy C. Chescheir, MD  
Editor-in-Chief

2018 IMPACT FACTOR: 4.965  
2018 IMPACT FACTOR RANKING: 7th out of 83 ob/gyn journals

---

In compliance with data protection regulations, you may request that we remove your personal registration details at any time. (Use the following URL: <https://www.editorialmanager.com/ong/login.asp?a=r>). Please contact the publication office if you have any questions.

August 15, 2019

Re: ONG-19-991 - Manuscript Revision- "Pregnancy-Associated Atypical Hemolytic Uremic Syndrome: A Systematic Review of Case Reports"

Attn: Dr. Nancy Chescheir, Editor, Obstetrics & Gynecology

Dear Dr. Chescheir,

Thank you for the opportunity to revise our manuscript ONG 19-991, "Pregnancy-Associated Atypical Hemolytic Uremic Syndrome: A Systematic Review of Case Reports".

We have carefully reviewed your email dated July 18th, 2019, enclosing your comments and the reviewers' comments of our manuscript. We have revised the manuscript according to these comments and we have provided our responses in a point-by-point manner. Revisions in the manuscript are updated using Tracked Changes feature in Microsoft Word. We hope the revised version is now suitable for publication in Obstetrics & Gynecology and we look forward to sharing this work with your readers.

Finally, as the lead author, I affirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained."

Sincerely,

Richard M. Burwick, MD, MPH

[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]

## **Authors' response to reviewers' comments**

### **-Reviewer 1**

*This is a systematic review that sought to evaluate the presentation, diagnosis, treatment and outcomes of gravid patients with atypical hemolytic uremic syndrome (p-aHUS), before and after eculizumab became available. After executing their search algorithm and reviewing the articles for inclusion, 48 case reports describing 60 unique cases of p-aHUS with a total of 66 total pregnancies. Twelve of these cases were patients with previous diagnosis of HUS and 54 were first episode cases. Most of the cases of first episode HUS were postpartum, and associated with many poor obstetrical outcomes, nearly the cases of known HUS preceding pregnancy had very poor outcomes. Eculizumab was associated with higher rates of disease remission after it became available. The authors conclude that p-aHUS usually presents in the postpartum period often following obstetrical complications and eculizumab is most effective for achieving disease remission. Ways in which this manuscript could be improved include:*

#### **Comment #1**

*Lines 202-203: What were the actual numbers of each of these obstetrical outcomes? I would enumerate here.*

**Author reply: We added data for the actual adverse outcomes as recommended on lines 202-203 –“... (2 maternal deaths, 7 end-stage renal disease or dialysis).”**

#### **Comment #2**

*Line 253: How easy is it to obtain complement genetic testing? What labs offer it? Again as a clinician, what do I need to know to order this lab?*

**Author reply: Complement genetic testing can be ordered as a send-out laboratory test. There are a few specialized laboratories across the country that offer this testing, and we have personally utilized Machaon Diagnostics in Oakland, CA. We prefer not to mention any specific company, in part because the studies referenced in this systematic review utilized a variety of different laboratories.**

**However, we did modify the text in the discussion for more guidance (paragraph 3) –**

**“TTP can be easily ruled out with an ADAMTS13 activity level <10% and the presence of autoantibodies. Likewise, complement genetic testing may be performed to support a diagnosis of aHUS, particularly when a pathogenic mutation is discovered. However, ADAMTS13 and complement genetic testing are send-out labs in most institutions, limiting turnaround time. To expedite diagnosis and treatment of aHUS, and to help rule out TTP**



**more quickly, it may be beneficial for clinicians to work with their laboratory medicine department and hospital leadership to review options for ADAMTS13 and complement genetic testing.”**

**Comment #3**

*Line 256: How widely available and costly is eculizumab? Were most of the cases managed with a multidisciplinary team? What does the practicing obstetrician need to know about starting and managing this drug?*

**Author reply: Thank you for your question.**

**Eculizumab is widely available because it is FDA-approved for aHUS, and also FDA approved for paroxysmal nocturnal hemoglobinuria (PNH) and myasthenia gravis (MG). Eculizumab is expensive and the cost is variable. Depending on the health care system, on-label use of the drug for inpatients may or may not be reimbursed. Outpatient reimbursement for on-label treatment can usually be achieved, but options for outpatient infusion may vary by insurance status.**

**Most cases of pregnancy-associated aHU are best managed by multidisciplinary teams including the primary ob-gyn, maternal fetal medicine, nephrology and hematology. Critical care doctors may also be involved for patients in the intensive care unit. The practicing obstetrician should know how to recognize and diagnose aHUS and should know that eculizumab is FDA approved for treatment. When obstetricians suspect a diagnosis of aHUS they should involve a care provider who has experience starting and managing the drug.**

**We added the following lines in the discussion-**

**End of paragraph 2 –**

**“When obstetricians suspect p-aHUS, they should involve other providers with expertise in diagnosing and treating aHUS, and this may include maternal fetal medicine, nephrology, hematology or critical care physicians.”**

**End of paragraph 4-**

**“Finally, it is important to note that eculizumab is a high-cost drug that may not be readily available at every institution and despite on-label use, insurance coverage may vary. Providers considering use of eculizumab should work with the pharmacy department to discuss drug access, inpatient cost considerations, and plan for outpatient infusions and long-term follow up.”**

## **Reviewer #2**

*Gupta and colleagues submit a systematic review from published case reports to "evaluate disease presentation, diagnosis, treatment, and clinical outcomes in women with pregnancy-associated atypical hemolytic uremic syndrome (p-aHUS), before and after eculizumab". This Reviewer would request the Authors to address the following:*

### **Comment #1**

*Line 27...In the Precis, Abstract and elsewhere in the manuscript, the Authors make the statement "eculizumab is most effective for achieving disease remission" in comparison to other treatment modalities. With this retrospective study design originating from published case reports, such a strong conclusion cannot be made, as timing, sequence and duration of treatment modalities cannot be compared. Their strong claim of eculizumab as the "most effective" of treatments should be toned-down.*

**Author reply:** Thank you for bringing this to our attention. We agree with the reviewers.

**To reduce the strength of the statement, we modified the Precis statement from "eculizumab is most effective for achieving disease remission" to "eculizumab is effective for achieving disease remission".**

**This change was also made throughout the manuscript.**

### **Comment #2**

*Line 60...The Authors describe atypical HUS; a brief differentiation from typical HUS would be of interest to the obstetrical Reader.*

**Author reply:** We added a line in the introduction (line 2) to define typical HUS in contrast to atypical HUS:

**"Atypical hemolytic uremic syndrome (aHUS) is a complement-mediated disorder, characterized by microangiopathic hemolysis, thrombocytopenia and renal failure. It should be distinguished from typical diarrhea-associated HUS, which is most commonly due to Shiga toxin-producing *E. coli*."**

### **Comment #3**

*Line 113...Are there any other monoclonal antibodies besides eculizumab used for p-aHUS?*

**Author reply:** There are no other monoclonal antibodies besides eculizumab that are FDA-approved for aHUS.

Comment #4

*Line 154...What date defines "the era after eculizumab"? A PubMed search shows the first publication with eculizumab was in 2002.*

**Author reply:** Thank you for your question. You are correct that eculizumab was first FDA approved for paroxysmal nocturnal hemoglobinuria (PNH) in 2007 prior to FDA approval for aHUS. We were using the term “era before and after eculizumab” in reference to the period before and after FDA approval of eculizumab for treatment of aHUS in 2011. We now realize that the term is a little confusing and so we removed all use of the word “era” in reference to eculizumab. We modified the text throughout the manuscript to state –

**“... before and after Food and Drug Administration approval of eculizumab for treatment of aHUS in 2011”.**

Comment #5

*Line 169...The acronym (TMA) for the term "thrombotic microangiopathy" should be spelled out at first use.*

**Author reply:** We spelled out “thrombotic microangiopathy (TMA)” at first mention in the introduction section of the manuscript (line 70). However, we wrote it out again on line 169 so that the reader can be reminded of the meaning.

Comment #6

*Line 229...What sequence of treatment do the Authors recommend for the diagnosis of p-aHUS during pregnancy or the postpartum period?*

**Author reply:** Thank you for this important question. It is difficult to diagnose and treat p-aHUS quickly because it often overlaps with pregnancy complications (preeclampsia, hemorrhage), and it may be mistaken for TTP. We wanted to recognize that a strict treatment approach may be difficult for these reasons. We modified the discussion (and added reference 70) as follows:

**“Atypical hemolytic uremic syndrome is a complement-mediated disorder that is best treated with complement blockade,<sup>69</sup> yet we found that plasma exchange was often utilized as a first-line option for p-aHUS, even following FDA approval of eculizumab. While the American Society for Apheresis states that the role of therapeutic plasma exchange in**

treatment of aHUS is not established,<sup>70</sup> the decision to start plasma exchange may be driven by the desire to treat TTP presumptively until it can be ruled out. Like aHUS, TTP is a life-threatening TMA disorder, but unlike aHUS, TTP is best treated with plasma exchange because it is usually due to ADAMTS13 autoantibodies.<sup>71,72, 73, 74</sup>

**...Until a diagnosis of p-aHUS can be made with reasonable certainty, the initial treatment approach should be made on a case-by-case basis. Once the diagnosis of p-aHUS is made, eculizumab should be considered for on-label treatment as it appears to improve long-term remission of disease when compared to women with p-aHUS not treated with eculizumab.”**

Comment #7

*Table 1...The Authors report a demographic variable of "Primip", which this Reviewer interprets as women who delivered their first child as a result of the index pregnancy. However these women would be nulliparous (i.e. Nullip) at the time of p-aHUS diagnosis if they had not yet delivered. Thus this term may be confusing to the Reader... (i.e. a primiparous woman has given birth to 1 child). Are they referring to the parity status after delivery in index cases? It may be better to report gravidity and or parity, in relationship to pre-delivery in each index pregnancy.*

**Author reply: Thank you for this comment. We had decided to use the term Primip because cases usually occurred postpartum in women delivering their first child. But we agree this may be a confusing term. Thus, we changed the variable to nulliparous (nullip), and made a footnote that this term refers to the pre-delivery status in the index pregnancy, as suggested by the reviewer.**

**Reviewer #3**

*The authors performed a systematic review of pregnancy-associated atypical hemolytic uremic syndrome (p-aHUS) case reports, to evaluate disease presentation, diagnosis, treatment, and clinical outcomes, before and after eculizumab.*

*The manuscript is well written and addresses a topic important to patients and multidisciplinary team of clinicians (e.g., Maternal-Fetal Medicine, Nephrology, Hematology, Critical Care).*

*What is already reviewed and available?*

*1. NEJM 2013 (reference 20) - A study that changed clinical practice*

*\*Eculizumab inhibited complement-mediated thrombotic microangiopathy and was associated with significant time-dependent improvement in renal function in patients with atypical hemolytic-uremic syndrome.*

*\*Eculizumab was associated with a significant improvement in health-related quality of life.*

**Author reply: Thank you, we agree this was a landmark paper showing benefit of eculizumab for treatment of aHUS**

*2. An excellent review and take-home message (reference 17), and case report (reference 68) by the authors;*

**Author reply: Thank you**

*3. Reports in Obstet Gynecol (references 23 and 60);*

**Author reply: Agree, prior publications in Obstet Gynecol supports ob-gyn interest in the topic**

*4. Others Reports in Hematology (reference 27) and Nephrology (reference 24)*

**Author reply: Agree, prior publications in Hematology and Nephrology shows broad interest in the topic to multiple disciplines.**

*What does this study added?*

*Discussion. Page 14 lines 272-276. Agreed*

**Author reply: Thank you, we sincerely appreciate the reviewer's positive comments**

#### ***Statistical editor comments***

Comment #1

*Tables 1, 2: These Tables could be placed in supplemental on-line material with a concise summary in main text. Need units for age.*

**Author reply: We appreciate the reviewer's comment, but we believe that Tables 1 and 2 are the main findings of the systematic review and we have a strong desire to include them in the main text. One important benefit is that the reader can easily review individual cases, and quickly find the associated reference. We are concerned that many readers receive the Green Journal in their home or office, and they may not seek out supplemental on-line material.**

**We have kept Table 1 and 2 in the main text for now, but if the editors agree that we should move them to supplemental material we are happy to do that.**

Comment #2

*Table 3, 4: Since the two cohorts had  $N = 37$  and  $N = 17$ , the precision cited for all %s should be rounded to nearest integer, not to 0.1% precision. Need units for maternal age, gestational age.*

**Author reply: Thank you, these changes have been made in Table 3 and 4 and corresponding data in Results section.**

Comment #3

*lines 126-127, Tables 3,4: Many of the comparisons involve 2x2 tables with some entries  $< 5$ . Those should have been tested with Fisher's test, not Chi-square. This will change the p-values of many entries. Should also specify what "non-parametric test of medians" was used.*

**Author reply: We apologize for the oversight on Fisher's exact testing and we have updated this data as appropriate for cell counts  $< 5$ . We updated test of medians to state Wilcoxon rank-sum test.**

Comment #4

*The comments re: prognosis may be influenced by selection bias, since these were all case reports that had been published and may not be a representative sample.*

**Author reply: Thank you, we agree. We had stated this as a limitation in the discussion but we modified the text for more clarity.**

**“There may be a publication bias towards cases with a positive outcome or an unusual feature, such as a newly described genetic variant. Thus, these cases may not be a fully representative sample.”**

### ***Editor's comments***

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

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

*- please add the Alexion Pharmaceuticals is the manufacturer of eculizumab.*

**Author reply: Change made in disclosure statement. “Dr. Burwick is on the speaker’s bureau for Alexion Pharmaceuticals, the manufacturer of eculizumab”**

*- in methods, please define atypical (as compared to typical) HUS*

**Author reply: We have update this in the methods section of the abstract, introduction section, and methods section of the main text:**

**“Atypical hemolytic uremic syndrome was defined by microangiopathic hemolysis, thrombocytopenia and renal failure and was distinguished from typical diarrhea-associated HUS, which is most commonly due to Shiga toxin-producing *E. coli*.”**

*- did you look for more rigorous types of studies, such as RCT's, retrospective cohort studies, etc? Would seem a shame to not have included these a limited to only case reports.*

**Author reply: Thank you for your comment. An extensive and vigorous search of the literature was performed according to PRISMA statement and we did not identify any RCT studies of p-aHUS subjects. There were two retrospective cohorts of p-aHUS subjects, but without individual data for inclusion and analysis. These case series were listed as exclusion #5 in methods section and study flow diagram (Figure 1).**

**We agree that wording in the abstract may suggest that we only reviewed case reports, so we modified the wording:**

**“Included English-language manuscripts describing atypical hemolytic uremic syndrome in pregnancy or postpartum. Atypical HUS was defined by hemolysis, thrombocytopenia and renal failure and was distinguished from diarrhea-associated HUS. Cases were excluded if individual data could not be obtained, the diagnosis was unclear, or an alternative etiology was more likely, such as thrombotic thrombocytopenic purpura or Shiga toxin-producing *E. coli*”**

*- Why would you include these 12 cases if you study is about atypical Pregnancy associated HUS?*

**Author reply:** This systematic review focused on pregnancy-associated aHUS rather than postpartum aHUS specifically. Our search looked for all women with aHUS in pregnancy or the postpartum period, whether the diagnosis was new or recurrent. We felt it was important to include both groups in this manuscript because they provide unique sets of data. Women with first-episode aHUS in the postpartum period often recover and then have questions about future pregnancy. We wanted to show data on pregnancy outcomes in women with known aHUS, to help guide other women and their care providers. This is the first manuscript to systematically review such cases and we hope to share the data.

*- Differentiate from HUS*

**Author reply:** We have updated the text in the introduction “Atypical hemolytic uremic syndrome (aHUS) is a complement-mediated disorder, characterized by microangiopathic hemolysis, thrombocytopenia and renal failure. It should be distinguished from typical diarrhea-associated HUS, which is most commonly due to Shiga toxin-producing *E. coli*”

*- please explain ADAMTS13 diagnostic role*

**Author reply:** We updated the text in methods and also discussion.

**Methods:** We also abstracted data for ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13), which is used to diagnose TTP (activity level <10%).

**Discussion:** “TTP can be easily ruled out with an ADAMTS13 activity level <10% and the presence of autoantibodies. Likewise, complement genetic testing may be performed to support a diagnosis of aHUS, particularly when a pathogenic mutation is discovered. However, ADAMTS13 and complement genetic testing are send-out labs in most institutions, limiting turnaround time. To expedite diagnosis and treatment of aHUS, and to help rule out TTP more quickly, it may be beneficial for clinicians to work with their laboratory medicine department and hospital leadership to review options for ADAMTS13 and complement genetic testing.”

*- Move this sentence to precede second sentence in this paragraph.*

**Author reply:** Revision made.

*- Since these labs are not obtained routinely, could you tell us the presenting symptoms or findings that prompted the laboratory testing?*



**Author reply: We added a line in the text:**

**“Laboratory testing was often triggered by symptoms such as nausea, vomiting, abdominal pain, headache, shortness of breath, or elevated blood pressure”**

*- Don't describe this as different eras. Prior to introduction of the drug and after, or pre and post 2011 are ok. Same is true throughout the manuscript. I Also, this implies that after 2011, eculizumab was always used. Is that true? You seem to be implying that women had different disease severity prior to vs after 2011. Why would you think so? Same question as it relates to sentence starting on line 161. I'm just not getting where you are going with this information couched this way.*

**Author reply: Yes, we meant prior to the FDA approval of eculizumab for treatment of aHUS in 2011. We agree that use of the term “era before eculizumab” is misleading, since eculizumab was approved for PNH in 2007. Thus, we have modified the text throughout the manuscript.**

**We chose to compare data on women treated with and without eculizumab, because eculizumab was the first FDA-approved drug for treatment of aHUS. We felt that this represented a major breakthrough for treatment of aHUS and we wanted to determine if this change influenced the way the disease was diagnosed and treated.**

**Prior to eculizumab, women were treated with either plasma exchange or dialysis, neither of which addressed the underlying etiology (complement activation). The American Society for Apheresis now states that the role of plasma exchange for aHUS is not established, and thus we added that statement and reference to the conclusion. We agree that the availability of ADAMTS13 is very helpful to rule out TTP and to separate the diagnoses of TTP and aHUS. Some providers still combine TTP-HUS but we now understand that the two are different diseases with different treatments.**

**While we don't want to over-emphasize eculizumab, it is the only FDA-approved drug for aHUS and we chose it for that reason.**

**We modified the discussion for more clarity:**

**“Atypical hemolytic uremic syndrome is a complement-mediated disorder that is best treated with complement blockade,<sup>69</sup> yet we found that plasma exchange was often utilized as a first-line option for p-aHUS, even following FDA approval of eculizumab. While the American Society for Apheresis states that the role of therapeutic plasma exchange in treatment of aHUS is not established,<sup>70</sup> the decision to start plasma exchange may be driven by the desire to treat TTP presumptively until it can be ruled out. Like aHUS, TTP is a life-threatening TMA disorder, but unlike aHUS, TTP is best treated with plasma exchange because it is usually due to ADAMTS13 autoantibodies.<sup>71, 72, 73, 74</sup> TTP can be**

easily ruled out with an ADAMTS13 activity level <10% and the presence of autoantibodies. Likewise, complement genetic testing may be performed to support a diagnosis of aHUS, particularly when a pathogenic mutation is discovered. However, ADAMTS13 and complement genetic testing are send-out labs in most institutions, limiting turnaround time. To expedite diagnosis and treatment of aHUS, and to help rule out TTP more quickly, it may be beneficial for clinicians to work with their laboratory medicine department and hospital leadership to review options for ADAMTS13 and complement genetic testing. Until a diagnosis of p-aHUS can be made with reasonable certainty, the initial treatment approach should be made on a case-by-case basis. Once the diagnosis of p-aHUS is made, eculizumab should be considered for on-label treatment as it appears to improve long-term remission of disease when compared to women with p-aHUS not treated with eculizumab.”

*- Do you mean "prior to 2011"?*

**Author reply:** Yes, we meant prior to the FDA approval of eculizumab for treatment of aHUS in 2011. We agree that use of the term “era before eculizumab” is misleading, since eculizumab was approved for PNH in 2007. Thus, we have modified the text throughout the manuscript.

*- As you are writing this, it seems that its the drug that was the driver behind the change in diagnostic testing. Wasn't it really the development and refinement of ADAMTS13 testing, independent of the drug. And again, "before and after eculilzumab" is engrandizing the introduction of this drug. Could you please provide the dates for the introduction and widespread uptake of ADAMTS13 testing as that seems way more relevant.*

**Author reply:** We agree that the introduction of ADAMTS13 helped to define TTP and to separate it from aHUS. This is very relevant and valuable. We believe that ADAMTS13 testing increased after eculizumab approval because eculizumab provided a significant change in the treatment approach (TTP- plasma exchange; aHUS- eculizumab). Although the benefit of plasma exchange for aHUS is unproven, it was often given for treatment of aHUS before 2011. Thus, ADAMTS13 testing prior to 2011 did not greatly change the treatment approach (plasma exchange was used for both TTP and aHUS). Once a better treatment option became available for aHUS in 2011 (FDA approval of eculizumab), providers began to understand the importance of differentiating TTP and aHUS.

We modified the discussion as noted above, to better discuss use of ADAMTS13 in TTP.

We also modified the text to emphasize importance of ADAMTS13 in ruling out TTP:

**“ADAMTS13 activity level was >10% in all 21 cases of p-aHUS in which it was tested, ruling out TTP. This emphasizes the value of ADAMTS13 testing to rule out TTP and to help expedite the diagnosis of aHUS.”**

**We could not determine when ADAMTS13 became available, but we updated the discussion to give a little more background on ADAMTS13 testing.**

**“Like aHUS, TTP is a life-threatening TMA disorder, but unlike aHUS, TTP is best treated with plasma exchange because it is usually due to ADAMTS13 autoantibodies.<sup>71, 72, 73, 74</sup> TTP can be easily ruled out with an ADAMTS13 activity level <10% and the presence of autoantibodies”**

*- what group makes up the "21" here.*

**Author reply: we modified the text for clarity:**

**“ADAMTS13 activity level was >10% in all 21 cases of p-aHUS in which it was tested, ruling out TTP.**

*- When was the diagnosis made? What I'm getting at, was the drug withheld until after delivery?*

**Author reply: To clarify that treatment was not withheld, we modified the text:**

**“In the majority (15/17, 88%) of cases of first-episode p-aHUS in which eculizumab was utilized, both diagnosis and treatment occurred in the postpartum period.”**

*- Please edit. As written, it reads that these 15 women reported the use of the standard dose. Perhaps, Of the 15 women treated....., the standard loading regimen was used in 12 (80%).....*

**Author reply: Text modified as recommended:**

**“Of the 15 women treated with eculizumab in the postpartum period, the standard loading regimen was used in 12 (80%) but was unspecified in 3 others. The standard maintenance regimen was used in 11 (73%), while the maintenance regimen was unspecified in two cases, reported as 900 mg IV twice weekly in one,<sup>33</sup> and 1200 mg IV monthly in another.<sup>62</sup>”**

*- Specify that this data is from non pregnant people.*

**Author reply: This change has been made**

*- Please temper this statement. While your data is compelling, this is all based on case reports which may result in a high degree of bias in the data. Here, and in each instance such as the precis and abstract, as well as the text, you need to avoid describing it as "most effective".*

**Author reply: We modified the language throughout the manuscript and modified the phrase “most effective” to simply “effective”. In the discussion, we modified the text as follows:**

**“Until a diagnosis of p-aHUS can be made with reasonable certainty, the initial treatment approach should be made on a case-by-case basis. Once the diagnosis of p-aHUS is made, eculizumab should be considered for on-label treatment as it appears to improve long-term remission of disease when compared to women with p-aHUS not treated with eculizumab”**

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

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

*3. As of December 17, 2018, Obstetrics & Gynecology has implemented an "electronic Copyright Transfer Agreement" (eCTA) and will no longer be collecting author agreement forms. When you are ready to revise your manuscript, you will be prompted in Editorial Manager (EM) to click on "Revise Submission." Doing so will launch the resubmission process, and you will be walked through the various questions that comprise the eCTA. Each of your coauthors will receive an email from the system requesting that they review and electronically sign the eCTA.*

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

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

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

**Statement added to the cover letter above.**

*5. Obstetrics & Gynecology follows the Good Publication Practice (GPP3)\* guideline for manuscripts that report results that are supported or sponsored by pharmaceutical, medical device, diagnostics and biotechnology companies. The GPP3 is designed to help individuals and organization maintain ethical and transparent publication practices.*

*(1) Adherence to the GPP3 guideline should be noted in the cover letter.*

*(2) For publication purposes, the portions of particular importance to industry-sponsored research are below. In your cover letter, please indicate whether the following statements are true or false, and provide an explanation if necessary:*

*(2a) All authors had access to relevant aggregated study data and other information (for example, the study protocol) required to understand and report research findings.*

*(2b) All authors take responsibility for the way in which research findings are presented and published, were fully involved at all stages of publication and presentation development and are willing to take public responsibility for all aspects of the work.*

*(2c) The author list accurately reflects all substantial intellectual contributions to the research, data analyses, and publication or presentation development. Relevant contributions from persons who did not qualify as authors are disclosed in the acknowledgments.*

*(2d) The role of the sponsor in the design, execution, analysis, reporting, and funding (if applicable) of the research has been fully disclosed in all publications and presentations of the findings. Any involvement by persons or organizations with an interest (financial or nonfinancial) in the findings has also been disclosed.*

*(2e) All authors have disclosed any relationships or potential competing interests relating to the research and its publication or presentation.*

*(3) The abstract should contain an additional heading, "Funding Source," and should provide an abbreviated listing of the funder(s).*

*(4) In the manuscript, a new heading—"Role of the Funding Source"—should be inserted before the Methods and contain a detailed description of the sponsor's role as well as the following language:*

*"The authors had access to relevant aggregated study data and other information (such as study protocol, analytic plan and report, validated data table, and clinical study report) required to understand and report research findings. The authors take responsibility for the presentation*

*and publication of the research findings, have been fully involved at all stages of publication and presentation development, and are willing to take public responsibility for all aspects of the work. All individuals included as authors and contributors who made substantial intellectual contributions to the research, data analysis, and publication or presentation development are listed appropriately. The role of the sponsor in the design, execution, analysis, reporting, and funding is fully disclosed. The authors' personal interests, financial or non-financial, relating to this research and its publication have been disclosed." Authors should only include the above statement if all of it is true, and they should attest to this in the cover letter (see #2, above).*

*\*From Battisti WP, Wager E, Baltzer L, Bridges D, Cairns A, Carswell CI, et al. Good publication practice for communicating company-sponsored medical research: GPP3. Ann Intern Med 2015;163:461-4.*

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

*7. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Review articles should not exceed 25 typed, double-spaced pages (6,250 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, tables, boxes, figure legends, and print appendixes) but exclude references.*

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

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

**- Abstract 300 words**

*9. Only standard abbreviations and acronyms are allowed. A selected list is available online at <http://edmgr.ovid.com/ong/accounts/abbreviations.pdf>. Abbreviations and acronyms cannot be*

*used in the title or précis. Abbreviations and acronyms must be spelled out the first time they are used in the abstract and again in the body of the manuscript.*

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

*11. Line 225: 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.*

***- Although we did perform a systematic review, we decided to remove line 225.***

*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](http://edmgr.ovid.com/ong/accounts/table_checklist.pdf).*

*13. Figure 1 may be resubmitted as-is.*

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

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

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

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

*Again, your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Aug 08, 2019, we will assume you wish to withdraw the manuscript from further consideration.*

*Sincerely,*

*Nancy C. Chescheir, MD  
Editor-in-Chief*