OBSTETRICS & GYNECOLOGY

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

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

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

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

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

Date: Dec 27, 2019
To: "Brett David Einerson" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-19-2205

RE: Manuscript Number ONG-19-2205

Reconsidering invasion: our experience with placenta accreta spectrum

Dear Dr. Einerson:

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

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

Your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Jan 17, 2020, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: Very well-written commentary with good use of surgical, ultrasonographic, and pathologic data to support new approach to characterization of placenta accreta spectrum. Are you able to propose specific, concise terminology to replace accreta/increta/percreta and depth of invasion? On lines 163-166 it appears that you have identified 3 main issues, but was wondering if there was specific terminology that you would recommend using for both clinical care and future research. If so a table comparing the old versus new terminology would be helpful.

Reviewer #2: Comments to the author:
I would suggest a reference to dehiscence vs. invasion with PAS in the title itself
The authors present a current commentary on the mechanism of PAS favoring a dehiscence process vs. the traditional description of invasion. The argument for this theory is well developed throughout the manuscript. The figures are clear however some are redundant and could be consolidated to make the teaching point. My main issue with the manuscript is how this differs or adds to the multiple citations carefully reviewed by the author on this theory? Specifically, the objectives were clear however I don't think they addressed prevention and treatment in any depth.

Abstract:
The abstract is well written, and the objectives are clear although not fully addressed in the body of the manuscript.

Introduction:

1. Line 51 The known increased RR of PAS with the number of cesarean section is well documented. Given the theory proposed, is there any information on type of uterine closure ie 1 vs 2 layers or type of suture.? Although controversial with uterine rupture and TOLAC it would be interesting to see if there is any association with PAS by closure. N Am J Med Sci. 2012 Aug; 4(8): 362-363.

2. Line 54 What theory is there for those "rare" cases that invaded outside the uterus? This contradicts your hypothesis.

3. Line 58 The citation #12 Am J Obstet Gynecol. 2018;218(1):75-87 was an extensive review of the literature with similar theories. How does this manuscript add to the review or management?

4. Line 91 Explain the institutional evolution of policies for handling PAS. Are they done with gyn/onc, stents, 34 weeks etc. All these multidisciplinary approaches have addressed the outcomes of interest.

Imaging:

5. Line 104-115 Is there any data on doppler heart rates on the various vessels perceived as maternal vs. fetal? If so one would expect all hyper vascular areas previously described as invasion in fact maternal proliferation due to angiogenesis as mentioned.

Figures:
6. #2 The sequential pictures are not very clear.

Histopathology:
7. Figure 8 I would suggest putting areas pointing to trophoblast and vascular spaces.

Conclusion:
8. 191-193 Explain how this theory changes prevention and treatment? It is not articulated in the paper. Perhaps lower cesarean section rates may help. Also, what specifically is changed on the surgical approach? It would be great to expand upon your teams' surgical approach and how it is supported by a dehiscence vs. an invasive theory of PAS.

Reviewer #3: This is an observational study aimed at assessing the cause of pathology seen in the spectrum of placenta accreta. Primarily this study is aimed at re-defining placenta accreta spectrum (PAS) as a disorder of the myometrium, versus a disorder of the placenta.

1. It would be great if the authors could provide the number of cases of placenta accreta seen at their institution, as well as the number of cases reviewed and utilized for this study. On line 82, a mention that 160 patients were reviewed, but was this only in regards to adhesive disease or were these cases also used to reflect the observations and conclusions of the author for this study.

2. The author states in line 55 that "abnormally attached placentas do not, in our option, grow and spread like a malignant tumor". It is important to consider the pathophysiology of trophoblastic cells. By their nature, trophoblast promote cell growth, migration and angiogenesis, and as evidenced by gestational trophoblastic disease, have the capacity to migrate and invade other tissue sources and behave / proliferate very similar to cancer when not contained within the uterus.

3. In the section for surgical observations, it was noted that erroneous classifications of placenta percreta, or protrusion past the serosa could be caused by surgical manipulation. It would be helpful for the author to report how well the gross findings correlate with the histopathologic diagnosis. Often, the gross diagnosis may prove to be less severe than the histopathologic diagnosis due to microscopic disease altering the diagnosis.

4. In regards to adhesive disease, it is unclear how adhesions would affect the diagnosis of PAS as this is usually confirmed by histopathology.

5. On line 93, the author notes that correlation with maternal morbidity "are note related to the depth of placental invasion per se". In cases where the myometrium is intact there is often still a significant risk for hemorrhage that may correlate more with the area and volume of placental adherence. Trophoblast tend to be angiogenic and promote enhanced vascularization which lead to bleeding and increased complications during surgery.

6. The author mentions that scare dehiscence was the cause for invasion. This may not take into account abnormal adherence that develops in areas other than previous scar sites, including posterior or fundal adherence for prior lower uterine segment incisions, then there are also cases of abnormal adherence in patients without prior cesarean delivery or serosal scars, which may not be accounted for based on this theory.

Associate Editor's Comments:

Please in your revision suggest with more specificity how rethinking the pathophysiology can alter clinical care, research, or both

EDITORIAL OFFICE COMMENTS:

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

2. As of December 17, 2018, Obstetrics & Gynecology has implemented an "electronic Copyright Transfer Agreement" (eCTA) and will no longer be collecting author agreement forms. When you are ready to revise your manuscript, you will be prompted in Editorial Manager (EM) to click on "Revise Submission." Doing so will launch the resubmission process, and

you will be walked through the various questions that comprise the eCTA. Each of your coauthors will receive an email from the system requesting that they review and electronically sign the eCTA.

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

3. 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.

4. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Current Commentary articles 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 print appendixes) but exclude references.

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

* All financial support of the study must be acknowledged.
* Any and all manuscript preparation assistance, including but not limited to topic development, data collection, analysis, writing, or editorial assistance, must be disclosed in the acknowledgments. Such acknowledgments must identify the entities that provided and paid for this assistance, whether directly or indirectly.
* All persons who contributed to the work reported in the manuscript, but not sufficiently to be authors, must be acknowledged. Written permission must be obtained from all individuals named in the acknowledgments, as readers may infer their endorsement of the data and conclusions. Please note that your response in the journal's electronic author form verifies that permission has been obtained from all named persons.
* If all or part of the paper was presented at the Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists or at any other organizational meeting, that presentation should be noted (include the exact dates and location of the meeting).

6. 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: Current Commentary articles, 250 words. Please provide a word count.

7. 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.

8. 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.

9. The Journal's Production Editor had the following to say about this manuscript:

"Figures 2 and 7: Please upload a version without A, B, and C labels. These will be added back per journal style. The arrows are okay."

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

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

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

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

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10. 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.

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

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

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

Again, your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Jan 17, 2020, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

The Editors of Obstetrics & Gynecology

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

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Dear Editors of *Obstetrics & Gynecology*,

Thank you for this opportunity to submit a revised draft of our manuscript (ONG-19-2205) titled "Reconsidering invasion: our experience with placenta accreta spectrum" to *Obstetrics & Gynecology*. We appreciate the work done by reviewers and editors to provide valuable feedback on our manuscript.

To prepare this re-submission, I read the Instructions for Authors guideline and specific instructions detailed in the decision email.

Below is a point-by-point response to reviewers' comments and concerns.

Sincerely,

Brett D. Einerson, MD MPH
University of Utah
January 17, 2020

Reviewer #1
Very well-written commentary with good use of surgical, ultrasonographic, and pathologic data to support new approach to characterization of placenta accreta spectrum.

- **Comment 1**: *Are you able to propose specific, concise terminology to replace accreta/increta/percreta and depth of invasion?*

  Response: We agree that new terminology to replace "accreta/increta/percreta" and "depth of invasion" are needed. However, we believe that proposing an alternative is outside the scope of this paper. Several groups, including a U.S. placenta accreta consortium, are working to develop evidence-based staging and grading terminologies that can be tested and improved over time – we are participating in these efforts and they will be published in forthcoming papers. In practice, we define the severity of suspected PAS according to the estimated risk for massive hemorrhage and resources necessary for the case. A full description of these changes over time in our practice would, in our opinion, distract from the central message of this commentary. But if requested by the editors, we are happy to include a few paragraphs describing our clinical practice.

  In response, we have added the following to the revised manuscript:
  "Diagnostic imaging and pre-operative staging can be improved over time by focusing on location and size of placental extension / uterine dehiscence, degree of pelvic hypervascularity, and extent of pelvic adhesive disease instead of focusing on surrounding organs that might be "invaded."

  and

  "***New terminology, developed over time and tested for clinical utility by a multi-***

center, multi-national group of PAS experts is needed."

- **Comment 2**: *On lines 163-166 it appears that you have identified 3 main issues, but was wondering if there was specific terminology that you would recommend using for both clinical care and future research. If so a table comparing the old versus new terminology would be helpful.*

  Response: Thank you for this thoughtful suggestion. New terminology should, in our opinion, be developed by a multi-center, multi-national group of investigators who can create, study, and revise classifications over time (similar to how cancers are graded, staged, studied, and reclassified). See Comment 1.

Reviewer #2

- **Comment 1**: *I would suggest a reference to dehiscence vs. invasion with PAS in the title itself. The authors present a current commentary on the mechanism of PAS favoring a dehiscence process vs. the traditional description of invasion.*

  Response: Thank you for this comment. If the editors prefer, we can make the title "Placenta accreta spectrum: uterine dehiscence, not placental invasion"

- **Comment 2**: *The argument for this theory is well developed throughout the manuscript. The figures are clear however some are redundant and could be consolidated to make the teaching point.*

  Response: We have consolidated points whenever possible in the revised manuscript.

- **Comment 3**: *My main issue with the manuscript is how this differs or adds to the multiple citations carefully reviewed by the author on this theory? Specifically, the objectives were clear however I don't think they addressed prevention and treatment in any depth.*

  Response: This is a very important point. Our manuscript, as a *Current Commentary,* is meant to summarize, amplify, and unify theories described by other investigators and provide representative pictorial evidence from our clinical experience to support an alternative way of talking about PAS. This call to action is important because the use of invasion, which is in our opinion inaccurate, is nearly ubiquitous and needs to change.

  To clarify the importance of this issue, we made the following revisions on line 42-46, and 57: "Depth of invasion" has become a common proxy for risk in treatment of PAS, and many societies and studies use "abnormally invasive placenta" to describe PAS. **"*In its latest obstetric care consensus document on PAS, ACOG uses invasion to describe and classify the disorder. Similarly, FIGO relies on descriptions of placental invasion to determine the grade of disease at the time of surgery. …New terminology is needed***."

  With regard to prevention and treatment, we have added the following to the revised manuscript, line 205-210: "***With a better understanding of how the placenta extends into the uterus and surrounding pelvic adhesions, the surgical approach can be modified to reduce the risk of massive hemorrhage by creating planes or margins that allow for placenta to be contained. Surgeons with a better understanding of the disease can***

communicate to pathologists the difference between the true disease in situ and the distorted appearance of the explanted uterus/placenta placed in the specimen bucket, thus improving surgical and pathologic staging. Research on the prevention of PAS can focus more on uterine factors (e.g. preventing primary cesareans, expanding access to vaginal birth after cesarean, and improving cesarean techniques and scar healing).”

- **Comment 4**: *The abstract is well written, and the objectives are clear although not fully addressed in the body of the manuscript.*

  Response: Thank you. We hope that we have more fully addressed the objectives in the body of the revised manuscript, particularly in the section entitled: ***“Why this matters”***

- **Comment 5**: *Line 51 The known increased RR of PAS with the number of cesarean section is well documented. Given the theory proposed, is there any information on type of uterine closure ie 1 vs 2 layers or type of suture.? Although controversial with uterine rupture and TOLAC it would be interesting to see if there is any association with PAS by closure. N Am J Med Sci. 2012 Aug; 4(8): 362-363.*

  Response: Thank you for this comment. We agree that reconsidering PAS as a uterine disorder requires a thorough evaluation of cesarean techniques and their association with PAS. This should be a key target for future research, though to our knowledge, no data are currently available on this topic.

  We highlight this important issue in the revised manuscript on line 210-212:
  “Research on the prevention of PAS can focus more on uterine factors (e.g. preventing primary cesareans, expanding access to vaginal birth after cesarean, and improving cesarean techniques and scar healing).”

- **Comment 6**: *Line 54 What theory is there for those "rare" cases that invaded outside the uterus? This contradicts your hypothesis.*

  Response: We discuss this later in the body of paper on lines 73-79. **“*In some cases, the serosa is replaced by or indiscernible from scar tissue in the area of prior uterine surgery. Even in these cases, the placenta is typically contained by the scar tissue itself. The trophoblast/placenta does not “invade” and obliterate serosa or adhesions. On postoperative pathological inspection the placenta may appear to protrude or “invade” beyond the uterine serosa, but this is the result of surgical manipulation during difficult dissection through dense scar tissue. In some cases, the apparent protrusion of placenta beyond the serosa is the result of uterine scar rupture during labor.”***

- **Comment 7**: *The citation #12 Am J Obstet Gynecol. 2018;218(1):75-87 was an extensive review of the literature with similar theories. How does this manuscript add to the review or management?*

  Response: Please see our response to Comment 3 above.

- **Comment 8**: *Explain the institutional evolution of policies for handling PAS. Are they done with gyn/onc, stents, 34 weeks etc. All these multidisciplinary approaches have addressed*

the outcomes of interest.

Response: We believe that a full description of how PAS is managed at our university is outside the scope of this manuscript, and has been published before (PMID: 29669225, 30299279). However, we have added the following to the revised manuscript regarding how surgical care may change with a right understanding of PAS: ***"With a better understanding of how the placenta extends into the uterus and surrounding pelvic adhesions, the surgical approach can be modified to reduce the risk of massive hemorrhage by creating planes or margins that allow for placenta to be contained."***

- **Comment 9**: *Line 104-115 Is there any data on doppler heart rates on the various vessels perceived as maternal vs. fetal? If so one would expect all hyper vascular areas previously described as invasion in fact maternal proliferation due to angiogenesis as mentioned.*

  Response: We are unaware of data specifically addressing this query. When needed, heart rate by doppler can be used to identify maternal versus fetal vessels.

- **Comment 10**: *Figures: #2 The sequential pictures are not very clear.*

  Response: Can the editors/reviewer clarify this comment? We believe the sequential images illustrate our point clearly. Does the reviewer mean that the resolution is suboptimal?

- **Comment 12**: *Conclusion: 191-193 Explain how this theory changes prevention and treatment? It is not articulated in the paper. Perhaps lower cesarean section rates may help. Also, what specifically is changed on the surgical approach? It would be great to expand upon your teams' surgical approach and how it is supported by a dehiscence vs. an invasive theory of PAS.*

  Response: Thank you for this comment, and the opportunity to clarify the importance of this Commentary. Please see in the revised manuscript the section ***"Why this matters."***

Reviewer #3

This is an observational study aimed at assessing the cause of pathology seen in the spectrum of placenta accreta. Primarily this study is aimed at re-defining placenta accreta spectrum (PAS) as a disorder of the myometrium, versus a disorder of the placenta.

- **Comment 1**: *It would be great if the authors could provide the number of cases of placenta accreta seen at their institution, as well as the number of cases reviewed and utilized for this study. On line 82, a mention that 160 patients were reviewed, but was this only in regards to adhesive disease or were these cases also used to reflect the observations and conclusions of the author for this study.*

  Response: This commentary relies on the collective experience of our center. We report in the revised manuscript: ***"In our group's experience, spanning more than 25 years and hundreds of PAS cases (now consistently 40-60 cases of PAS annually), we…"***

- **Comment 2**: *The author states in line 55 that "abnormally attached placentas do not, in our option, grow and spread like a malignant tumor". It is important to consider the pathophysiology of trophoblastic cells. By their nature, trophoblast promote cell growth, migration and angiogenesis, and as evidenced by gestational trophoblastic disease, have*

the capacity to migrate and invade other tissue sources and behave / proliferate very similar to cancer when not contained within the uterus.

Response: Thank you for this important comment. We agree that trophoblastic cells are invasive, migrate, and promote angiogenesis as a part of normal placentation. We also agree that trophoblastic cells can act malignantly, as in gestational trophoblastic disease. But in cases of PAS, we contend that trophoblasts do not act malignantly and the placenta cannot be reasonably viewed as an invasive organ. We nod to this concept: "*Indeed, normal pregnancy with normal placentation involves the invasion of extravillous trophoblasts into uterine spiral arteries. The interaction of the decidua and trophoblasts prevents the trophoblasts from moving farther into the myometrium. When the decidua is absent, the extravillous trophoblasts behave in the same way, but do so in the myometrium rather than remaining confined to the endometrium (Figures 8 and 9)*."

We added clarification in the revised manuscript: ***"Trophoblasts do not act like a malignant cells in PAS, as they do in choriocarcinoma. They act normally in an abnormal space, and with abnormal access to uterine scar, adhesions, and pelvic vessels."***

- **Comment 3**: *In the section for surgical observations, it was noted that erroneous classifications of placenta percreta, or protrusion past the serosa could be caused by surgical manipulation. It would be helpful for the author to report how well the gross findings correlate with the histopathologic diagnosis. Often, the gross diagnosis may prove to be less severe than the histopathologic diagnosis due to microscopic disease altering the diagnosis.*

  Response: Thank you for this comment. Understanding the correlation between intra-operative findings, gross pathologic findings, and microscopic/histopathologic findings is a critical step in better understanding, grading/staging, and treating PAS. As far we are aware, there are no published data to inform an answer to this query. Our site is enrolling patients in a radiology / surgery / pathology correlation study to understand that correlation better. We hope to report the findings of this study in the next year.

- **Comment 4**: *In regards to adhesive disease, it is unclear how adhesions would affect the diagnosis of PAS as this is usually confirmed by histopathology.*

  Response: Adhesive disease is undoubtedly an important contributor to hemorrhagic and operative morbidity in PAS surgery. In the revised manuscript, we have clarified how adhesive disease – though not part of traditional histopathologic grading– is an integral and understudied contributor to grading/staging/severity of PAS.

  In the revised manuscript we added: "***Another important contributor to morbidity during PAS surgery that is not captured in the pathologic grading of PAS is adhesive disease***. In a review of 160 patients with more than two cesareans, 43% developed significant adhesions following the primary cesarean delivery. Of the 57% who had not developed significant adhesions after the primary cesarean delivery, 37% had significant adhesions at the third surgery. Perioperative risks associated with adhesive disease and repeat cesarean delivery include bleeding, bowel injury or obstruction, hysterectomy, and prolonged operative times and hospital stays, all of which are similar to those encountered with PAS. ***Dense pelvic adhesive disease can make PAS surgery difficult and morbid,***

even when even when extension of the placenta is mild."

- **Comment 5**: *On line 93, the author notes that correlation with maternal morbidity "are note related to the depth of placental invasion per se". In cases where the myometrium is intact there is often still a significant risk for hemorrhage that may correlate more with the area and volume of placental adherence. Trophoblast tend to be angiogenic and promote enhanced vascularization which lead to bleeding and increased complications during surgery.*

  Response: Thank you for this comment. We too have experienced cases in which placental extension is not severe but hypervascularity is still impressive.

  Our manuscript emphasizes that area of involvement (degree of dehiscence) and abnormal vasculature are important contributors to morbidity in the following lines 101-106: "*morbidity and difficulty are related to (1) the integrity of the myometrium in the area of placental attachment (i.e., the degree of uterine scar dehiscence), (2) the degree and location of pelvic adhesive disease which impedes safe access to avascular dissection planes, and (3) the extent of abnormal vasculature in and around hysterectomy planes."*

- **Comment 6**: *The author mentions that scare dehiscence was the cause for invasion. This may not take into account abnormal adherence that develops in areas other than previous scar sites, including posterior or fundal adherence for prior lower uterine segment incisions, then there are also cases of abnormal adherence in patients without prior cesarean delivery or serosal scars, which may not be accounted for based on this theory.*

  Response: Thank you for this comment. We argue that the primary pathologic defect in PAS is the absence of decidua (anywhere in the uterus), not necessarily a large cesarean defect. In cases where transmural extension does not occur, trophoblastic attachment occurs (adherence) but dehiscence does not. This is discussed in the section on Histopathology Observations:

  "The primary histopathologic abnormality in PAS is the absence of intervening decidua basalis at the site of implantation ***anywhere in the uterus****. Decidual defects are usually—but not always—the result of uterine surgery or instrumentation. …When the decidua is absent, the extravillous trophoblasts behave in the same way, but do so in the myometrium rather than remaining confined to the endometrium… The severity of PAS is, therefore, not determined primarily by the invasive properties of the trophoblast/placenta, but by the extent of the uterine scar (transmural scars producing more severe cases) and the depth of trophoblastic attachment within the scar/niche in relation to the myometrial depth."*

Associate Editor

- **Comment**: *Please in your revision suggest with more specificity how rethinking the pathophysiology can alter clinical care, research, or both*

  Response: Thank you for the opportunity to clarify the importance of this manuscript. Please see the subsection ***"Why this matters"*** in the revised manuscript:

  "Adopting an understanding of PAS as a disorder of defective decidua, abnormal attachment, uterine dehiscence, and pelvic hypervascularity – not placental invasion

– will help direct research efforts and clinical resources toward the prevention, accurate diagnosis, and safe treatment of this devastating and increasingly common disorder. Diagnostic imaging and pre-operative staging can be improved over time by focusing on location and size of placental extension / uterine dehiscence, degree of pelvic hypervascularity, and extent of pelvic adhesive disease instead of focusing on surrounding organs that might be "invaded." This gives clinicians and surgeons better information upon which to make clinical decisions. Risk stratification and delivery timing may be optimized if researchers can identify uterine and pelvic factors (aside from "depth of invasion") that predispose patients to unscheduled deliveries and preterm bleeding events. With a better understanding of how the placenta extends into the uterus and surrounding pelvic adhesions, the surgical approach can be modified to reduce the risk of massive hemorrhage by creating planes or margins that allow for placenta to be contained. Surgeons with a better understanding of the disease can communicate to pathologists the difference between the true disease in situ and the distorted appearance of the explanted uterus/placenta placed in the specimen bucket, thus improving surgical and pathologic staging. Research on the prevention of PAS can focus more on uterine factors (e.g. preventing primary cesareans, expanding access to vaginal birth after cesarean, and improving cesarean techniques and scar healing). In sum, we will be distracted and ineffective in preventing, treating, and classifying PAS if we continue to talk about and conceptualize it as a disorder of placental invasion. New terminology, developed over time and tested for clinical utility by a multi-center, multi-national group of PAS experts is needed."

Editorial Office

- **Comment**: *If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online.*

  Response: We opt-in.

- **Comment**: *Current Commentary articles 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 print appendixes) but exclude references.*

  Response: The revised manuscript word count, including figure legends, is 2,647.

- **Comment**: *The word limits for different article types are as follows: Current Commentary articles, 250 words. Please provide a word count.*

  Response: Word count (72) is now listed on the Title Page.

- **Comment**: *The Journal's Production Editor had the following to say about this manuscript: "Figures 2 and 7: Please upload a version without A, B, and C labels. These will be added back per journal style. The arrows are okay."*

  Response: Certainly. Thank you.