

OBSTETRICS & GYNECOLOGY



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

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

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obgyn@greenjournal.org.

Date: Dec 17, 2021
To: "Brock E Polnaszek" [REDACTED]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-21-2328

RE: Manuscript Number ONG-21-2328

Pathologic assessment of the placenta—Science versus tradition

Dear Dr. Polnaszek:

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).

Please be sure to address the Editor comments (see "EDITOR COMMENTS" below) in your point-by-point response.

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 07, 2022, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: This provocative critique asks the question "Why do we send placentas for pathological examination" and answers that the rationale is hazy at best.

In particular, the framing with umbilical cord blood gasses (though brought in very late) is helpful. Placental pathology should be thought of as a laboratory test, and should be "Chose[n] Wisely".

This article raises critical questions and raises the real problem that CAP guidelines are >30 years old, confusing, and not being followed. However I believe a revision will make this article more robust. I have one general comment, which is that pediatricians are also potential consumers of placental pathology findings. While this is an obstetrics journal, their perspective should be considered and relevant literature identified and cited.

I have some specific questions and critiques, as well as material that I think would be valuable for inclusion.

Line 61: Please report and comment upon the ACOG guideline for placental examination.

Line 64-68?: The quote from CAP is not closed.

Lines 68-71: While the CAP's statement is dubious, the data presented to not falsify it. Specifically, the authors do not demonstrate that the release of the CAP guidelines caused an increase in the rate of placental examination. The lack of a comparison group between with/without placental examination makes secular trends in preterm birth, stillbirth, and litigiousness a poor datapoint. Globally, those parts of the world that lack placental pathology also tend to have the highest rates of stillbirth, however it would be absurd to argue that the lack of placental pathology causes the high rates of stillbirth.

Line 71: The statement "associative correlations between placental pathologic findings and clinical outcomes remain weak to non-existent.²¹" - is poorly substantiated by the citation. It should be moved to be with its supporting evidence, ~line 105.

Additional material for the "Why We Do What We Do?" section:

Odiibo I, Gehlot A, Ounpraseuth ST, Magann EF. Pathologic examination of the placenta and its clinical utility: a survey of obstetrics and gynecology providers. J Matern Fetal Neonatal Med. 2016;29(2):197-201. PMID: 25567565

Who make 2 points:

1. Only 36% of obstetricians surveyed are aware of the CAP guideline - this undermines the statement of the importance of the CAP guidelines.

And

2. Only 21% of obstetricians state that they understand pathology nomenclature "all of the time" - Do the authors feel this is a problem? To what extent is that lack of clinical utility of placental examination due to confusion about the meaning?

Line 74: "How Predictive Are Placental Abnormalities of Long-Term Adverse Neurologic Outcomes?" - this focus is overly narrow. e.g. Catov et al. found that maternal vascular malperfusion changes in placentas from patients _without_ hypertensive disorder in pregnancy were associated with an increased maternal cardiovascular risk (<https://doi.org/10.1111/1471-0528.15040>).

Line 77-78: The focus on population-based studies is poorly motivated. Laboratory tests tend to be justified on the basis of selected studies. I would consider it a favor if the authors would mention some of the challenges of wide-scale studies on the placenta, such as variation in nosology across institutions and time and challenges in extracting and pathologic diagnoses.

Line 79-82: Readers may find it valuable to specify the methodologic limitations described by Nelson and Blair so they may improve their critical thinking and study evaluation skills.

Line 98 / Table 3: The CPP, while an important study, is subject to several limitations. Several "chapters" of placental pathology are either barely represented (maternal vascular malperfusion outside of large infarcts), or missed entirely (fetal vascular malperfusion, chronic placental inflammation, perivillous fibrin deposition). Reference to the Amsterdam Criteria would not be amiss here (<https://doi.org/10.5858/arpa.2015-0225-CC>). As such the rationale for reproducing a large chunk of the CPP findings in Table 3 is unclear at best.

Line 135: The statement "because adverse outcomes, even in high-risk cohorts tend to occur infrequently, more children without a given lesion will generally have adverse outcomes than those with that lesion." - depends entirely on the risk of adverse outcomes and the prevalence of particular lesions. For example, in our cohort, stillbirth after SARS-CoV-2 infection is very rare, 1:100. "Covid placentitis", the mixture of chronic histiocytic intervillitis and massive perivillous fibrin deposition that has been associated with viral infection of the syncytiotrophoblast is also very rare, 1:100. But, of those with stillbirth, 3/4 had covid placentitis.

Additional material for: How Predictive Are Placental Abnormalities of Long-Term Adverse Neurologic Outcomes? Systematic review of adverse perinatal outcomes and placental pathology (from 2014, but quite large): <https://doi.org/10.1371/journal.pone.0089419>

Line 156: "Such placental findings are generally of very low specificity in determining the actual cause of death, and will only rarely have implications for subsequent clinical care." This statement is not supported by the literature, which has found that placental pathology is the single most useful test for determining cause of death (<https://doi.org/10.1016/j.ajog.2015.08.049>, doi: 10.1097/AOG.0000000000001937). In the 2nd study, placental pathology was found useful in 64% of cases, as compared to 12% for karyotype and 0.4% for parvovirus testing. The comparison to other laboratory tests is again a useful framing. The authors may chose to make a case for "...rarely have implicates for subsequent clinical care" with sufficient support from the literature.

Line 165: "this type of detail is rarely reported in standard pathologic evaluations;" In my view, this argues for quality improvement in placental pathology rather than not submitting it. Given that most studies on the utility of placental pathology use examinations performed by subspecialty perinatal pathologists, do the authors feel that sub specialization is important?

Line 194: Questioning Clinical Practice articles typically include an "alternatives" section here. Please provide one. Or, if there are no alternative, explain why not.

Line 197: Note that CAP guidelines are not binding on obstetricians.

Line 205 / Table 4: We are asked to substitute the judgement of the author(s) for that of CAP/ACOG. A more appropriate call would be for an update to guidelines, which has not occurred in >30 years (for CAP) and consideration of ACOG guidelines on how to manage specific placental pathologic diagnoses.

Reviewer #2:

The authors present a "questioning clinical practice" evaluating the utility of placental pathology.

Evaluating the evidence and need for placental pathology is interesting, clinically useful and may lead to more cost effective medicine. However the authors should present more detail to support their arguments.

Clinical Vignette- The vignette brings up a likely common scenario. Line 39 appears to include a great deal of opinion in the vignette.

Current Practice:

Line 42- the author's conclusions state that the practices surveyed are following current guidelines from the college of American Pathologist. This area should be extended to discuss what the current guidelines are and the indications for evaluation.

Why do we do what we do:

Line 64- please elaborate on the reasoning behind the description of the recommendation as "unsubstantiated."

Line 68- these statements seem to be more appropriate for later in the manuscript. This section should focus on evidence to support pathologic evaluation of the placenta.

The next section discusses the predictive value of placental pathology on neurologic outcomes. They focus on the predictive value of placentas and long term neurologic sequelae. The authors should elaborate on indications for placental pathology and how they may be clinically relevant and then question the literature. The use of the placental pathology to predict childhood outcomes may not be the best example for indications for placental pathology.

Please include some data on how pathology is used to make decisions regarding patients care. In what settings would this be useful and is the literature strong or weak in regards to that question?

Line 132- the summary line pertains only to their argument that it is not useful to predict adverse childhood outcomes and neurologic outcomes.

Line 148-154 please supply data that counseling regarding recurrence risk following adverse pregnancy outcomes does not incorporate placental pathology in regards to placenta accreta, severe malperfusion, and chorioamnionitis?

Line 158- this statement needs a reference.

Line 177- The description of the nature of the medical-legal system in the U.S. appears to be conjecture.

Line 179- The personal statement of "having reviewed hundreds of such cases" needs more solid data.

What are the Monetary Costs of Formal Placental Evaluation?

The discussion of CPT codes and technical and professional fees can be cut down.

Do the authors have any data on potential benefits of placental evaluation that may decrease costs in other areas (ie. Alterations in care in a subsequent pregnancy resulting in avoidance of NICU stay, awareness of risk of placenta accreta based on prior pathology resulting in decreased morbidity at subsequent cesarean and preparedness for hysterectomy).

Please address if alternatives exists? (as noted in the instructions for authors)

The Bottom Line:

Line 200- does reference 49 support this statement (conclusion from article is that 82% of placentas were appropriately sent to pathology)?

Reviewer #3: In this work, the authors address the issue of why we do what we do as it pertains to submission of the placenta for pathologic examination. The following questions and comments are raised:

It is notable that placental pathology was performed in 28% to 47% of cases at the academic centers versus 18% to 28% in community hospitals. Do the authors think this is a true and appropriate difference? Is a rate of up to 48% warranted in academic centers, which presumably are delivering patients of higher acuity, more likely to meet current criteria for placental evaluation?

It is worth noting that noting that all placental examinations are probably not equal. The likelihood of a significant finding is probably related to the attention and expertise of the pathologist.

Given the fact there are currently fewer placentas that are submitted for pathologic evaluation than would be eligible based on the CAP guidelines, do the authors feel that many clinicians and institutions have already narrowed their indications for placental pathology?

As a fetal organ, and the arbiter of nutrient and oxygen transport from mother to fetus, it is rational to expect there to be abnormalities in placental structure which would affect its function. with subsequent detrimental effects on the fetal

condition. Is the pathology at a level we are unable to detect? Are current techniques too unsophisticated to reveal the causes of fetal compromise? Or, is the placenta truly not etiologic in most cases of fetal/neonatal morbidity and mortality? Either way, it supports the notion of restricting current recommendations for examination by a pathologist.

EDITOR COMMENTS:

1. The Editors of Obstetrics & Gynecology have increased 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. When you submit your revised manuscript, please make the following edits to ensure your submission contains the required information that was previously omitted for the initial double-blind peer review:

- * Include your title page information in the main manuscript file. The title page should appear as the first page of the document. Add any previously omitted Acknowledgements (ie, meeting presentations, preprint DOIs, assistance from non-bylane authors).
- * Funding information (ie, grant numbers or industry support statements) should be disclosed on the title page and in the body text. For industry-sponsored studies, the Role of the Funding Source section should be included in the body text of the manuscript.
- * Include clinical trial registration numbers, PROSPERO registration numbers, or URLs at the end of the abstract (if applicable).
- * Name the IRB or Ethics Committee institution in the Methods section (if applicable).
- * Add any information about the specific location of the study (ie, city, state, or country), if necessary for context.

3. Obstetrics & Gynecology uses an "electronic Copyright Transfer Agreement" (eCTA), which must be completed by all authors. When you uploaded your manuscript, each co-author received an email with the subject, "Please verify your authorship for a submission to Obstetrics & Gynecology." Please check with your coauthors to confirm that they received and completed this form, and that the disclosures listed in their eCTA are included on the manuscript's title page.

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

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

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

6. Provide a précis on the second page, for use in the Table of Contents. The précis is a single sentence of no more than 25 words that states the conclusion(s) of the report (ie, the bottom line). The précis should be similar to the abstract's conclusion. Do not use commercial names, abbreviations, or acronyms in the précis. Please avoid phrases like "This paper presents" or "This case presents."

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. 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.

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

In addition, the American College of Obstetricians and Gynecologists' (ACOG) documents are frequently updated. These documents may be withdrawn and replaced with newer, revised versions. If you cite ACOG documents in your manuscript, be sure the references you are citing are still current and available. Check the Clinical Guidance page at <https://www.acog.org/clinical> (click on "Clinical Guidance" at the top). If the reference is still available on the site and isn't listed as "Withdrawn," it's still a current document.

If the reference you are citing has been updated and replaced by a newer version, please ensure that the new version supports whatever statement you are making in your manuscript and then update your reference list accordingly (exceptions could include manuscripts that address items of historical interest). If the reference you are citing has been withdrawn with no clear replacement, please contact the editorial office for assistance (obgyn@greenjournal.org). In most cases, if an ACOG document has been withdrawn, it should not be referenced in your manuscript.

11. Each supplemental file in your manuscript should be named an "Appendix," numbered, and ordered in the way they are first cited in the text. Do not order and number supplemental tables, figures, and text separately. References cited in appendixes should be added to a separate References list in the appendixes file.

12. 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 <https://wkauthorservices.editage.com/open-access/hybrid.html>.

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.

If you choose open access, you will receive an Open Access Publication Charge letter from the Journal's Publisher, Wolters Kluwer, and instructions on how to submit any open access charges. The email will be from publicationservices@copyright.com with the subject line, "Please Submit Your Open Access Article Publication Charge(s)." Please complete payment of the Open Access charges within 48 hours of receipt.

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

- * A confirmation that you have read the Instructions for Authors (<http://edmgr.ovid.com/ong/accounts/authors.pdf>), and
- * A point-by-point response to each of the received comments in this letter. Do not omit your responses to the Editorial Office or Editors' comments.

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

Again, your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Jan 07, 2022, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Jason Wright, MD
Editor-in-Chief, Elect

2020 IMPACT FACTOR: 7.661
2020 IMPACT FACTOR RANKING: 3rd out of 83 ob/gyn journals

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Maternal-Fetal Medicine
Department of Obstetrics and Gynecology
Women & Infants Hospital

Jason Wright, MD
Editor-in-Chief
Obstetrics & Gynecology

January 1st 2022

Re: ONG-21-2328R1

Dear Dr. Wright:

Thank you for your ongoing consideration of our "Questioning Clinical Practice" manuscript entitled "Pathologic assessment of the placenta—Evidence versus tradition" to be published with *Obstetrics and Gynecology*. Attached you will find the updated manuscript with track changes and a point-by-point response to the queries.

Reviewer #1: This provocative critique asks the question "Why do we send placentas for pathological examination" and answers that the rationale is hazy at best. In particular, the framing with umbilical cord blood gasses (though brought in very late) is helpful. Placental pathology should be thought of as a laboratory test, and should be "Chose[n] Wisely". This article raises critical questions and raises the real problem that CAP guidelines are >30 years old, confusing, and not being followed. However I believe a revision will make this article more robust. I have one general comment, which is that pediatricians are also potential consumers of placental pathology findings. While this is an obstetrics journal, their perspective should be considered and relevant literature identified and cited. I have some specific questions and critiques, as well as material that I think would be valuable for inclusion.

Thank you for these excellent points. We have added additional information from the neonatology literature. Lines 116-120

Line 61: Please report and comment upon the ACOG guideline for placental examination.

We have added more information regarding ACOG's once published guideline (a Clinical Opinion which is no longer endorsed) on placental examination from the year 1993 as well as their recommendation in the stillbirth practice bulletin. Lines 88-100

Line 64-68?: The quote from CAP is not closed.

Now closed: Lines 103-106

Lines 68-71: While the CAP's statement is dubious, the data presented to not falsify it. Specifically, the authors do not demonstrate that the release of the CAP guidelines caused an increase in the rate of placental examination. The lack of a comparison group between with/without placental examination makes secular trends in preterm birth, stillbirth, and litigiousness a poor datapoint. Globally, those parts of the world that lack placental pathology also tend to have the highest rates of stillbirth, however it would be absurd to argue that the lack of placental pathology causes the high rates of stillbirth.

We agree. As we highlight in the paper, tracking the number of placentas that are sent for pathologic assessment is difficult to ascertain both pre- and post-CAP guidelines. We found that even institutionally, these were not tracked well until recent years and that the ability to share this information within and across institutions, particularly as it relates to cost, was met with resistance. We surveyed more institutions than those that responded to our survey. To this point, the CAP's statement of the proposed benefits has not been upheld for either developed or under developed countries. We attempted to communicate both of these points more clearly in this paragraph. Lines 85-139

Line 71: The statement "associative correlations between placental pathologic findings and clinical outcomes remain weak to non-existent.²¹" - is poorly substantiated by the citation. It should be moved to be with its supporting evidence, ~line 105.

We have removed this statement.

Additional material for the "Why We Do What We Do?" section:

Odibo I, Gehlot A, Ounpraseuth ST, Magann EF. Pathologic examination of the placenta and its clinical utility: a survey of obstetrics and gynecology providers. J Matern Fetal Neonatal Med. 2016;29(2):197-201. PMID: 25567565

Who make 2 points:

1. Only 36% of obstetricians surveyed are aware of the CAP guideline - this undermines the statement of the importance of the CAP guidelines.

And

2. Only 21% of obstetricians state that they understand pathology nomenclature "all of the time" - Do the authors feel this is a problem? To what extent is that lack of clinical utility of placental examination due to confusion about the meaning?

Thank you for these important comments. We have added a section to the "Why We Do What We Do" portion of the manuscript, incorporating this reference along with perspective from our neonatology colleagues. Lines 110-139

Line 74: "How Predictive Are Placental Abnormalities of Long-Term Adverse Neurologic Outcomes?" - this focus is overly narrow. e.g. Catov et al. found that maternal vascular malperfusion changes in placentas from patients _without_ hypertensive disorder in pregnancy were associated with an increased maternal cardiovascular risk (<https://doi.org/10.1111/1471-0528.15040>).

Thank you for this comment. We specifically narrowed our article to focus on adverse neonatal

neurologic morbidity to reflect what clinicians reported as their primary and secondary indications for sending the placenta for examination (i.e. adverse outcomes and medical legal) as outlined by Odibo. The Catov study, although potentially important, has not prompted public health recommendations or, therefore, decreases in maternal morbidity or mortality.

Line 77-78: The focus on population-based studies is poorly motivated. Laboratory tests tend to be justified on the basis of selected studies. I would consider it a favor if the authors would mention some of the challenges of wide-scale studies on the placenta, such as variation in nosology across institutions and time and challenges in extracting and pathologic diagnoses. Line 79-82: Readers may find it valuable to specify the methodologic limitations described by Nelson and Blair so they may improve their critical thinking and study evaluation skills.

We agree that these studies are important and challenging to conduct. We have highlighted the specific methodologic limitations when available, including those described by Nelson and Blair. Lines 145-154

Line 98 / Table 3: The CPP, while an important study, is subject to several limitations. Several "chapters" of placental pathology are either barely represented (maternal vascular malperfusion outside of large infarcts), or missed entirely (fetal vascular malperfusion, chronic placental inflammation, perivillous fibrin deposition). Reference to the Amsterdam Criteria would not be amiss here (<https://doi.org/10.5858/arpa.2015-0225-CC>). As such the rationale for reproducing a large chunk of the CPP findings in Table 3 is unclear at best.

Thank you for this point. We felt that this study was historically too important to not cite and include in this questioning clinical practice. We have also highlighted the several limitations that have been published of population-health and placenta pathology research. We kept this in our paper as it continues to be used to assess and promote pathologic assessment of the placenta (e.g., as recently as the early 2000s a group compared specific placental lesions by race in the CPP).

We did add a section regarding the Amsterdam Criteria as an important step in pathologic assessment of the placenta that addresses several of the reviewer's comments above. Lines 135-139

Line 135: The statement "because adverse outcomes, even in high-risk cohorts tend to occur infrequently, more children without a given lesion will generally have adverse outcomes than those with that lesion." - depends entirely on the risk of adverse outcomes and the prevalence of particular lesions. For example, in our cohort, stillbirth after SARS-CoV-2 infection is very rare, 1:100. "Covid placentitis", the mixture of chronic histiocytic intervillitis and massive perivillous fibrin deposition that has been associated with viral infection of the syncytiotrophoblast is also very rare, 1:100. But, of those with stillbirth, 3/4 had covid placentitis.

Thank you for this comment and important finding. The specific clinical scenario of both stillbirth and SARS-CoV-2 infection is of course timely. We added your specific point to highlight that we are speaking "in general" and that our article focuses on adverse long-term neurologic outcomes.

Perhaps the SAR-CoV-2 infection placental lesions will ultimately be shown to be as important as the recommendations for placental evaluation after stillbirth, but again, this is a very select and specific cohort/example.

Additional material for: How Predictive Are Placental Abnormalities of Long-Term Adverse Neurologic Outcomes?

Systematic review of adverse perinatal outcomes and placental pathology (from 2014, but quite large): <https://doi.org/10.1371/journal.pone.0089419>

Thank you for this article. This review highlights several of the points we already discuss in our article. It also highlights conclusions on the limitations of these studies as neurologic outcomes are not always present after birth and long after placenta has been discarded. In that review, the findings have inconsistent results. We did add this systematic review to the evidence-based section as it does provide a nice summation of the available associations. Lines 211-219

Line 156: "Such placental findings are generally of very low specificity in determining the actual cause of death, and will only rarely have implications for subsequent clinical care." This statement is not supported by the literature, which has found that placental pathology is the single most useful test for determining cause of death (<https://doi.org/10.1016/j.ajog.2015.08.049> , doi: 10.1097/AOG.0000000000001937). In the 2nd study, placental pathology was found useful in 64% of cases, as compared to 12% for karyotype and 0.4% for parvovirus testing. The comparison to other laboratory tests is again a useful framing. The authors may chose to make a case for "...rarely have implicates for subsequent clinical care" with sufficient support from the literature. We agree that pathologic examination of the placenta in the case of stillbirth is important. Lines 99-100, 254-257

Line 165: "this type of detail is rarely reported in standard pathologic evaluations;" In my view, this argues for quality improvement in placental pathology rather than not submitting it. Given that most studies on the utility of placental pathology use examinations performed by subspecialty perinatal pathologists, do the authors feel that sub specialization is important? Thank you for this comment. Likely sub-specialization is important if placental pathology findings are to be reproducible. We have tried to add places in the paper to highlight the lack of clarity amongst and within obstetricians/clinicians, neonatologists, and pathologists including a reference to the Amsterdam criteria. Lines 110-139

Line 194: Questioning Clinical Practice articles typically include an "alternatives" section here. Please provide one. Or, if there are no alternative, explain why not.

We have added a purposed alternative solution and reason why this would be challenging and likely of limited benefit. Lines 297-324

Line 197: Note that CAP guidelines are not binding on obstetricians.

We acknowledge this. Line 328

Line 205 / Table 4: We are asked to substitute the judgement of the author(s) for that of CAP/ACOG. A more appropriate call would be for an update to guidelines, which has not occurred in >30 years (for CAP) and consideration of ACOG guidelines on how to manage specific placental pathologic diagnoses..

We have modified our text to suggest/support this statement and call on the CAP and ACOG to update their guidelines. Additionally we have removed Table 4. Line 332-337

Reviewer #2:

The authors present a "questioning clinical practice" evaluating the utility of placental pathology. Evaluating the evidence and need for placental pathology is interesting, clinically useful and may lead to more cost effective medicine. However the authors should present more detail to support their arguments.

Clinical Vignette- The vignette brings up a likely common scenario. Line 39 appears to include a great deal of opinion in the vignette.

Thank you for this point. We kept this vignette the same as we felt it best communicated the results that only 36% of physicians are aware of CAP guidelines based on the survey data.

Current Practice:

Line 42- the authors conclusions state that the practices surveyed are following current guidelines from the college of American Pathologist. This area should be extended to discuss what the current guidelines are and the indications for evaluation. We reference the guidelines/indications in Tables 1 and 2 from CAP and the Royal College. We also added information from ACOG throughout the manuscript on the presence or lack thereof information for pathologic assessment of the placenta. Lines 90-100

Why do we do what we do:

Line 64- please elaborate on the reasoning behind the description of the recommendation as "unsubstantiated."

We feel that to date, pathologic assessment of the placenta under the CAP guidelines and the promises of "quantifiable improvements in rates of prematurity, incidence of neurodevelopmental dysfunction from antepartum/intrapartum events, perinatal death rate, and malpractice costs" have not lived up to the promise of the guidelines.

Line 68- these statements seem to be more appropriate for later in the manuscript. This section should focus on evidence to support pathologic evaluation of the placenta.

We kept this section as we think that it provides the indications or proposed indications for why we perform pathologic examination of the placenta (i.e. the reported benefits of decreasing adverse outcomes such as preterm birth, etc.).

The next section discusses the predictive value of placental pathology on neurologic outcomes. They focus on the predictive value of placentas and long term neurologic sequelae. The authors should elaborate on indications for placental pathology and how they may be clinically relevant and then question the literature. The use of the placental pathology to predict childhood outcomes may not be the best example for indications for placental pathology.

We originally focused on long-term neurologic outcome as the ultimate, clinical goal of every pregnancy is a healthy and intact baby and seemed to be the most relevant to clinicians practicing obstetrics. For example, Odibo found that the top two reasons clinicians send the placenta are due to an adverse outcome or medical-legal concerns. Furthermore, nearly three quarters of clinicians in the 2015 ACOG professional liability survey had at least one claim and of those with a claim, 27.4% were regarding adverse neurologic morbidity. We also chose to focus on long-term childhood outcomes as this is one of the promises inherent in the CAP guidelines to “decrease rates of prematurity, cerebral palsy, and costs.” Lines 103-109

Please include some data on how pathology is used to make decisions regarding patients care. In what settings would this be useful and is the literature strong or weak in regards to that question?

We have included this data under the section “In What Situations or Conditions are Placental Abnormalities Useful for Subsequent Pregnancy Management After an Adverse Obstetric Outcome? In this section we include the lesions that are most likely to recur according to a leading placental pathologist and the clinical utility in understanding stillbirth Lines 234-290

Line 132- the summary line pertains only to their argument that it is not useful to predict adverse childhood outcomes and neurologic outcomes.

We have added neurologic outcome as a descriptor to better support our summary line. Line 145-154 and 332-337

Line 148-154 please supply data that counseling regarding recurrence risk following adverse pregnancy outcomes does not incorporate placental pathology in regards to placenta accreta, severe malperfusion, and chorioamnionitis?

While these recurrence risks found on placental pathology are useful, we argue that clinically these diagnoses are managed the same in the next pregnancy based on the clinical course. For example, preterm birth regardless of the etiology, includes cervical length screening and/or supplemental progesterone, regardless of the presence or absence of placental pathology that demonstrates there was chorioamnionitis. In fact, placenta pathology isn’t mentioned in the American College of

Obstetricians and Gynecologists Practice Bulletin 234, last updated in August 2021, for the prediction and prevention of spontaneous preterm birth nor is it mentioned in the American College of Obstetricians and Gynecologists committee opinion on intra-amniotic infection. We have added this section to support our argument. Lines 251-252

Line 158- this statement needs a reference.

This statement has been modified with references. Lines 251-258

Line 177- The description of the nature of the medical-legal system in the U.S. appears to be conjecture.

Thank you for this comment. We have added a citation to support the increasing medical-legal cases against obstetricians including the 2015 ACOG 2015 liability survey that demonstrated three quarters of clinicians had at least one professional disability claim and the most common was 27.4% regarding neurologic morbidity/mortality. Additionally, clinicians reported their primary and secondary rankings for sending the placenta for examination were adverse outcomes and medical legal concerns. Line 285

Line 179- The personal statement of "having reviewed hundreds of such cases" needs more solid data.

Thank you for this comment. We have included citations from medical-legal witnesses who are also in agreement with this statement/sentiment. Lines 287-288

What are the Monetary Costs of Formal Placental Evaluation?

The discussion of CPT codes and technical and professional fees can be cut down. Do the authors have any data on potential benefits of placental evaluation that may decrease costs in other areas (ie. Alterations in care in a subsequent pregnancy resulting in avoidance of NICU stay, awareness of risk of placenta accreta based on prior pathology resulting in decreased morbidity at subsequent cesarean and preparedness for hysterectomy).

We have cut down this section. The data on costs associated with pathologic assessment of the placenta were difficult to obtain and are largely extrapolated from CPT code. We could not find any cost-analysis strategies that have been performed to address the reviewer's comments. However, we agree that a cost-analysis piece would be interesting and timely to inform our call for ACOG and CAP guidelines.

Please address if alternatives exists? (as noted in the instructions for authors)

We have added the only alternative we found in the literature when conducting our literature review. Lines 297-324

The Bottom Line:

Line 200- does reference 49 support this statement (conclusion from article is that 82% of

placentas were appropriately sent to pathology)?

We have included the survey data that suggest only 34% of providers are aware of CAP guidelines.

Reviewer #3: In this work, the authors address the issue of why we do what we do as it pertains to submission of the placenta for pathologic examination. The following questions and comments are raised:

It is notable that placental pathology was performed in 28% to 47% of cases at the academic centers versus 18% to 28% in community hospitals. Do the authors think this is a true and appropriate difference? Is a rate of up to 48% warranted in academic centers, which presumably are delivering patients of higher acuity, more likely to meet current criteria for placental evaluation?

Thank you for this excellent point. We agree with your thoughts that this may represent a higher acuity of patients delivered at academic centers which meet criteria by CAP guidelines (e.g. premature delivery, maternal disease comorbidity) but there are also several other explanations that are speculative (e.g. placental pathologist present, costs, institutional/group practice pattern) and thus not added to the text. Regardless this range of pathologic assessment does warrant further exploration.

It is worth noting that noting that all placental examinations are probably not equal. The likelihood of a significant finding is probably related to the attention and expertise of the pathologist.

This is an excellent point and we agree. The placental pathology literature has made note of this as well and calls for specialized training and has made uniform steps to try and make placenta pathology lesions and reporting of lesions standardized (i.e. Amsterdam criteria).

Given the fact there are currently fewer placentas that are submitted for pathologic evaluation than would be eligible based on the CAP guidelines, do the authors feel that many clinicians and institutions have already narrowed their indications for placental pathology?

However, several explanations are plausible including clinician guided narrowing within a practice, acuity of patients between academic versus private/community hospitals, on site access to pathologists with placental specific training, or education of clinicians/providers on CAP guidelines.

As a fetal organ, and the arbiter of nutrient and oxygen transport from mother to fetus, it is rational to expect there to be abnormalities in placental structure which would affect its function. with subsequent detrimental effects on the fetal condition. Is the pathology at a level we are unable to detect? Are current techniques too unsophisticated to reveal the causes of fetal compromise? Or, is the placenta truly not etiologic in most cases of fetal/neonatal morbidity and mortality? Either way, it supports the notion of restricting current recommendations for examination by a pathologist.

Thank you for these thought provoking questions. We agree and hope our article prompts these exact

questions in those who read it and who develop guidelines.

EDITOR COMMENTS:

1. The Editors of Obstetrics & Gynecology have increased 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.

2. When you submit your revised manuscript, please make the following edits to ensure your submission contains the required information that was previously omitted for the initial double-blind peer review:

*** Include your title page information in the main manuscript file. The title page should appear as the first page of the document. Add any previously omitted Acknowledgements (ie, meeting presentations, preprint DOIs, assistance from non-byline authors).**

*** Funding information (ie, grant numbers or industry support statements) should be disclosed on the title page and in the body text. For industry-sponsored studies, the Role of the Funding Source section should be included in the body text of the manuscript.**

*** Include clinical trial registration numbers, PROSPERO registration numbers, or URLs at the end of the abstract (if applicable).**

*** Name the IRB or Ethics Committee institution in the Methods section (if applicable).**

*** Add any information about the specific location of the study (ie, city, state, or country), if necessary for context.**

We have included this information.

3. Obstetrics & Gynecology uses an "electronic Copyright Transfer Agreement" (eCTA), which must be completed by all authors. When you uploaded your manuscript, each co-author received an email with the subject, "Please verify your authorship for a submission to Obstetrics & Gynecology." Please check with your coauthors to confirm that they received and completed this form, and that the disclosures listed in their eCTA are included on the manuscript's title page.

Done

4. Standard obstetric and gynecology data definitions have been developed through the

reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions. Please access the obstetric data definitions at <https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-obstetrics-data-definitions> and the gynecology data definitions at <https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-gynecology-data-definitions>. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

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

- * All financial support of the study must be acknowledged.**
- * Any and all manuscript preparation assistance, including but not limited to topic development, data collection, analysis, writing, or editorial assistance, must be disclosed in the acknowledgments. Such acknowledgments must identify the entities that provided and paid for this assistance, whether directly or indirectly.**
- * All persons who contributed to the work reported in the manuscript, but not sufficiently to be authors, must be acknowledged. Written permission must be obtained from all individuals named in the acknowledgments, as readers may infer their endorsement of the data and conclusions. Please note that your response in the journal's electronic author form verifies that permission has been obtained from all named persons.**
- * If all or part of the paper was presented at the Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists or at any other organizational meeting, that presentation should be noted (include the exact dates and location of the meeting).**
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6. Provide a précis on the second page, for use in the Table of Contents. The précis is a single sentence of no more than 25 words that states the conclusion(s) of the report (ie, the bottom line). The précis should be similar to the abstract's conclusion. Do not use commercial names, abbreviations, or acronyms in the précis. Please avoid phrases like "This paper presents" or "This case presents."

We have included a precis that is 21 words.

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.

Thank you for this reference.

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.

Thank you, we have inserted and/or throughout our text.

9. 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.

Thank you. Our tables fit with this checklist.

10. Please review examples of our current reference style

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

In addition, the American College of Obstetricians and Gynecologists' (ACOG) documents are frequently updated. These documents may be withdrawn and replaced with newer, revised versions. If you cite ACOG documents in your manuscript, be sure the references you are citing are still current and available. Check the Clinical Guidance page at <https://www.acog.org/clinical> (click on "Clinical Guidance" at the top). If the reference is still available on the site and isn't listed as "Withdrawn," it's still a current document.

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Thank you for this information.

11. Each supplemental file in your manuscript should be named an "Appendix," numbered, and ordered in the way they are first cited in the text. Do not order and number supplemental tables, figures, and text separately. References cited in appendixes should be added to a separate References list in the appendixes file.

We have only one appendix, based on hospitals surveyed.

12. 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 <https://wkauthorservices.editage.com/open-access/hybrid.html>. 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. If you choose open access, you will receive an Open Access Publication Charge letter from the Journal's Publisher, Wolters Kluwer, and instructions on how to submit any open access charges. The email will be from publicationservices@copyright.com with the subject line, "Please Submit Your Open Access Article Publication Charge(s)." Please complete payment of the Open Access charges within 48 hours of receipt.

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