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.
RE: Manuscript Number ONG-19-1805

Abnormal Placental Growth Factor and the Risk of Adverse Neonatal and Maternal Outcomes

Dear Dr. Parchem:

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 14 days from the date of this letter. If we have not heard from you by Nov 21, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: The article submitted is about a secondary analysis of the PETRA study; it is an interesting theme (preeclampsia is still shrouded in controversy regarding its pathophysiology and way of management).

It is well written and it is interesting; I raise some questions regarding the article in question:

Regarding the composite neonatal outcome why is not at least included severe fetal growth restriction?

Regarding the results section is there any possible explanation for the reason why women with low PLGF are enrolled with a later gestational age?; why was it chosen (for the first and last time in the article) the cut-off 30pg/ml for the perinatal deaths?

I am not sure if lines 203-208 are truly important for the article, due to its low numbers and absence of significance

Regarding table 3 - I am not sure if the "other maternal complication" adds anything to the article

Regarding table 5 - I believe that only the overall numbers are meaningful; the majority of the others are too low to add any conclusion

The discussion is interesting; however I believe that it is important to to give more emphasis to the fact that even though results are significant (both composite maternal and neonatal outcomes) the majority (for example 90,8% of women with low PLGF did not have the composite neonatal outcome) did not have any of them. I believe it should be more emphasized the fact that a normal PLGF has a strong association with normal outcomes. It should also be emphasized that 43% of the women with normal PLGF had a preeclampsia with severe features. The clinical meaning of PLGF in preeclampsia is still not completely understood.

Reviewer #2: The main issue of the manuscript is the following:

1. There is an overstatement based on their results.

2. It is important to consider the difference between the statistical significance and the clinical applicability. The authors' conclusion is that "PGIF is a robust indicator of adverse neonatal and maternal outcomes." However, how can they make
this statement when the false positive rate of their test is approximately 90%? See composite outcomes.

3. Based on the results of this manuscript, how can we apply it to patients with preeclampsia to usefully predict outcome?

4. My main suggestion to the authors is to determine the MoM rather than using two cutoffs, based on the fact that the PGIF changes with advancing gestation.

Reviewer #3: The authors present a secondary analysis of the previously published older PETRA trial - a prospective multi-center observational trial studying women with suspected preeclampsia. This was an investigator initiated trial funded by Alere who purportedly had no input into investigation and analysis. The study examines the relationship between low or extremely low PGIF with adverse composite neonatal and maternal outcomes.

These results are not new and have been seen in several trials in the UK. The authors state that their findings are more generalizable to the US and more diverse.

In the abstract, line 62, just say that the composite neonatal outcome did not occur in any of the normal PGIF pregnancies, "not 0%".

Line 75, modify sentence to "iatrogenic preterm delivery".

It is clear you mean to compare potential differences in findings when cases were classified according to 2013 definitions versus 2019 ACOG guidelines although your explanation in line 131 does not make sense nor does line 187 in the results section.

Line 137, I'm not sure that differentiating between gestational hypertension with severe range blood pressures and superimposed preeclampsia and preeclampsia with severe features is necessary or pertinent to the study.

Similarly, in line 137, the sentence discussing the divisions of superimposed preeclampsia can be eliminated as it does not impact the study nor does it add to the manuscript.

Line 221, the meaning of this sentence referencing shortened interval delivery is unclear.

Ultimately, the problem with this study is that it is still investigational and PGIF is not available clinically.

Reviewer #4: The authors have conducted a secondary analysis of the PETRA Trial in an attempt to determine whether PGIF is associated with adverse neonatal and maternal outcomes in women with a suspected or confirmed diagnosis of preeclampsia. This was a well-conducted study and the manuscript was well-written. While abnormally low PGIF was associated with composite adverse neonatal outcomes in the population of patients that were studied, the clinical implications are uncertain. I don't believe that this information is available, but I would be curious to see if there was correlation with low PGIF values and ultrasound abnormalities (e.g. abnormal umbilical artery Doppler, abnormal BPP, etc). Does a low PGIF in and of itself identify patients at higher risk for an adverse neonatal or maternal outcome or is this seen in association with other parameters that may predict the same? I agree that while the information gleaned from this study may be important and clinically valuable, use of PGIF as a clinical tool should be subjected to a randomized trial as the authors suggest to ascertain its true clinical utility. I would like to know how the authors arrived at the cut offs for low (less than or equal to 100 pg/mL) and very low (< 12 pg/mL) PGIF values. This seems like an arbitrary definition.

STATISTICAL EDITOR COMMENTS:

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

Table 1: There are statistically significant differences in mean GA for the cohorts, but apparently there was no adjustment of PGIF level for GA.

Table 2: The aRR adjustment used 6 variables (lines 146-151), while the counts for adverse outcomes were 68 and 3 for the composite. This is an unfavorable ratio of variables used as adjustors vs the counts of adverse outcomes, which was also true for many of the other comparisons for Low PGIF. These are likely over fitted to the data. Similarly, for the very
low PIGF, the counts were 58 and 13, still too few for precise adjustment.

Table 3: Similar issue with aRRs and low counts (low PIGF had 7 and 46 counts of composite adverse), while very low PIGF had 34 and 19 for adverse composite events.

Although the use of RR and aRRs are useful, many of the aRRs in the study are based on insufficient counts and are not reliable estimates. Many readers would likely find expression of composite adverse events for Low or very low PIGF categories useful if expressed in terms of sensitivity and specificity, each with appropriate CIs.

ASSOCIATE EDITOR COMMENTS:

We feel that the clinical value of these data as presented would be subject to misinterpretation, specifically with reference to the adjusted risks.

To wit, if I understand correctly, using a threshold of 100, ~2/3 of patients would be classified as having a low value. And although they have an increased risk of the composite neonatal outcome, 90% of these "abnormal values" are not associated with the composite outcome.

Likewise, with the threshold of 12, still ~ 1/3 of patients would be considered to have an abnormal value, and of these women, >80% of these values are not associated with the adverse neonatal composite.

So in your revision, please move away from relative risks and present data in terms of sensitivity and specificity with 95% CIs.

Thank you.

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. 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 organizations 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).


4. On your STROBE checklist, please indicate the page number where each item appears. You may write this in the margin of the checklist.

5. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology 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.

6. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Original Research reports should not exceed 22 typed, double-spaced pages (5,500 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and print appendices) but exclude references.

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

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

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

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

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

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

11. In your Abstract, manuscript Results sections, and tables, the preferred citation should be in terms of an effect size,
such as odds ratio or relative risk or the mean difference of a variable between two groups, expressed with appropriate confidence intervals. When such syntax is used, the P value has only secondary importance and often can be omitted or noted as footnotes in a Table format. Putting the results in the form of an effect size makes the result of the statistical test more clinically relevant and gives better context than citing P values alone.

If appropriate, please include number needed to treat for benefits (NNTb) or harm (NNTh). When comparing two procedures, please express the outcome of the comparison in U.S. dollar amounts.

Please standardize the presentation of your data throughout the manuscript submission. For P values, do not exceed three decimal places (for example, "P = .001"). For percentages, do not exceed one decimal place (for example, 11.1").

12. 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.

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

14. 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 reference you are citing is still current and available. If the reference you are citing has been updated (ie, 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 (exceptions could include manuscripts that address items of historical interest). All ACOG documents (eg, Committee Opinions and Practice Bulletins) may be found via the Clinical Guidance & Publications page at https://www.acog.org/Clinical-Guidance-and-Publications/Search-Clinical-Guidance.

15. Figure 1: Please review the n values (624-580=44).

The other figures may be resubmitted with the revision as-is.

16. 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.

17. 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 14 days from the date of this letter. If we have not heard from you by Nov 21, 2019, 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

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.
November 17, 2019

Nancy C. Chescheir, MD
Editor-in-Chief

Obstetrics & Gynecology


Dear Dr. Chescheir,

Thank you for the opportunity to revise our manuscript. We appreciate the constructive comments from reviewers and editors. The comments are addressed in a point-by-point response below. Relevant changes in the text are highlighted in the document using “track changes” and referenced in the response using the line numbers of the revised manuscript. We have also attached the STROBE guidelines as requested. We confirm adherence to the GPP3 guideline.

As the lead author, I have read the Instructions for Authors and 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 have been explained.

We confirm that all of the following statements are true:
- All authors had access to relevant aggregated study data and other information (for example, the study protocol) required to understand and report research findings.
- 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.
- 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.
- 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.
- All authors have disclosed any relationships or potential competing interests relating to the research and its publication or presentation.

All authors have approved this revision. We hope the revised version is suitable for publication in Obstetrics & Gynecology. Thank you for your consideration.

Sincerely,

Jacqueline G. Parchem, MD
Response to *Obstetrics & Gynecology* Decision Letter for Manuscript Number ONG-19-1805

REVIEWER COMMENTS:

**Reviewer #1:**
The article submitted is about a secondary analysis of the PETRA study; it is an interesting theme (preeclampsia is still shrouded in controversy regarding its pathophysiology and way of management).

It is well written and it is interesting; I raise some questions regarding the article in question:

1. Regarding the composite neonatal outcome why is not at least included severe fetal growth restriction?

   **Response:** Although we agree that fetal growth restriction is an important and common finding in pregnancies complicated by hypertensive disorders, we did not include it in the composite neonatal outcome because the diagnosis relies on estimated fetal weight which is imprecise, varies by reference growth chart used, and often does not correlate with actual birth weight percentiles (Poljak et al, *Ultrasound Obstet Gynecol* 2016, doi: 10.1002/uog.17211). We instead report small-for-gestational-age birth weight, which more accurately identifies neonates at risk for complications.

2. Regarding the results section is there any possible explanation for the reason why women with low PLGF are enrolled with a later gestational age?

   **Response:** The reasons for the difference in mean gestational age of enrollment are unclear. Women were enrolled in PETRA between 20 and 41 weeks based on qualifying signs/symptoms without knowledge of PlGF result.

3. Why was it chosen (for the first and last time in the article) the cut-off 30pg/ml for the perinatal deaths?

   **Response:** For all cases of perinatal death, PLGF was <30 pg/ml. This was mentioned to describe the data and did not represent a separate cutoff that was studied. We have removed this parenthetical note for clarity.

4. I am not sure if lines 203-208 are truly important for the article, due to its low numbers and absence of significance

   **Response:** We thank the reviewer for this comment. The paragraph pertaining to outcomes for women who were not diagnosed with a hypertensive disorder was retained in the revised version of the manuscript as these results provide preliminary evidence to support the hypothesis that PLGF is a biomarker for placental function and thus may be associated with adverse outcomes irrespective of hypertensive diagnosis. We believe these findings may be of interest to some readers.
5. Regarding table 3 - I am not sure if the "other maternal complication" adds anything to the article

**Response:** We agree that “other maternal complications” includes very rare complications of preeclampsia, however, these data were retained for readers who may be interested in the frequency of severe maternal complications, such as stroke.

6. Regarding table 5 - I believe that only the overall numbers are meaningful; the majority of the others are too low to add any conclusion

**Response:** We have revised Table 5 to show only the overall numbers; the remaining data are now presented with the supplemental content (Appendix 2) for readers interested in the overlap between hypertensive diagnosis, SGA, and PIGF.

7. The discussion is interesting; however I believe that it is important to give more emphasis to the fact that even though results are significant (both composite maternal and neonatal outcomes) the majority (for example 90.8% of women with low PLGF did not have the composite neonatal outcome) did not have any of them. I believe it should be more emphasized the fact that a normal PLGF has a strong association with normal outcomes. It should also be emphasized that 43% of the women with normal PLGF had a preeclampsia with severe features. The clinical meaning of PLGF in preeclampsia is still not completely understood.

**Response:** Thank you. We agree that more emphasis should be given to the high sensitivity and negative predictive value of PIGF. The reviewer’s point that 43% of women with a normal PLGF were diagnosed with preeclampsia with severe features highlights a major challenge in the field – the diagnosis itself is imprecise and may be less predictive of adverse outcome than PIGF (Chappell et al, *Circulation* 2013, doi:10.1161/CIRCULATIONAHA.113.003215). We have added a new supplemental table (Appendix 3) with test performance characteristics (sensitivity, specificity, positive and negative predictive values), and revised the Abstract, Results (lines 242-248), and Discussion (lines 308-316) to modify the emphasis as suggested. A paragraph in the Discussion (lines 308-316) now reads:

“Perhaps the most compelling result of this study is the high negative predictive value of PLGF. The strong association between normal PLGF and a very low risk of serious adverse outcomes is consistent with prior research. Although PIGF has a low specificity and positive predictive value, it is worth noting that we currently rely on inferior clinical predictors of adverse outcome, such as blood pressure and maternal symptoms. We speculate that PIGF could be helpful in common cases of clinical uncertainty, such as differentiating superimposed preeclampsia from chronic hypertension exacerbation and distinguishing pathologic fetal growth restriction from constitutional smallness. Additionally, the availability of a blood test that is highly sensitive for stillbirth could potentially be used to inform fetal surveillance plans.”
Reviewer #2:
The main issue of the manuscript is the following:

1. There is an overstatement based on their results. It is important to consider the difference between the statistical significance and the clinical applicability. The authors' conclusion is that "PGIF is a robust indicator of adverse neonatal and maternal outcomes." However, how can they make this statement when the false positive rate of their test is approximately 90%? See composite outcomes.

Response: We appreciate the reviewer's comment and agree that the conclusion quoted here may be misleading given the high false positive rate. This language has been revised in the Précis and Abstract (lines 74-77). We also agree that the clinical applicability is uncertain. The study was designed to assess the relationship between PlGF and adverse outcomes, not to determine the clinical applicability of the test; therefore statements regarding clinical utility would be premature. We have added information regarding test performance in a new supplemental table (Appendix 3).

2. Based on the results of this manuscript, how can we apply it to patients with preeclampsia to useful predict outcome?

Response: Low PlGF has a high sensitivity and negative predictive value for adverse outcomes. Since the definitions and diagnostic criteria for preeclampsia and its subtypes are not precise, an objective test like PlGF has the potential to aid in risk stratification. We speculate the potential benefits of PlGF, if validated in clinical trials, therefore could include: reductions in the use of unnecessary maternal and fetal monitoring, laboratory testing, activity restrictions, hospitalization, iatrogenic preterm delivery, and anxiety for those with low risks of decompensation. However, the clinical impact of PlGF testing was not studied in PETRA or this analysis, and any claim to improved care or outcomes would be speculative. We have stated in the Discussion (lines 345-346): “randomized trials including U.S. women will be required to determine the value of PlGF as an adjunct to current management....”

3. My main suggestion to the authors is to determine the MoM rather than using two cutoffs, based on the fact that the PGIF changes with advancing gestation.

Response: The cutoffs used in the study are established and have been used in several other analyses, including PETRA (Barton et al., Am J Obstet Gynecol 2019, doi:10.1016/j.ajog.2019.09.003). Saffer and colleagues reported the 5th and 10th percentiles of PlGF from 20 to 40 weeks in 247 uncomplicated subjects using the Alere Triage PlGF assay, and found that between 20 to 35 weeks, the variance in the 5% percentile was less than 3.5% of the dynamic range (5th percentile 76 pg/ml at < 24 weeks to 141 pg/ml at 24 to 29 weeks; Saffer et al, Pregnancy Hypertension 2013, doi:10.1016/j.preghy.2013.01.004). Using the same PlGF assay, Chappell and colleagues found that 100 pg/ml was a clinically useful cutoff for the prediction of preeclampsia in women presenting between 20 and 35 weeks with virtually the same test performance as using gestational age-specific cutoffs (5th percentile; Chappell et al, Circulation 2013, doi:10.1161/CIRCULATIONAHA.113.003215). Additionally, other reports using the ratio of sFlt-1:PlGF have determined that a single cutoff may be used for accurate prediction of preeclampsia instead of gestational week specific values (Zeisler et al,
The Introduction states (lines 103-104): “Although PlGF varies by gestational age, absolute cutoffs have been adopted in many studies instead of percentile-for-gestational-age cutoffs because similar test performance has been reported.”

Reviewer #3:
The authors present a secondary analysis of the previously published older PETRA trial - a prospective multi-center observational trial studying women with suspected preeclampsia. This was an investigator initiated trial funded by Alere who purportedly had no input into investigation and analysis. The study examines the relationship between low or extremely low PlGF with adverse composite neonatal and maternal outcomes.

1. These results are not new and have been seen in several trials in the UK. The authors state that their findings are more generalizable to the US and more diverse.

Response: Thank you for recognizing the lack of data from the US. Given examples in obstetrics when results from the UK and other countries were not replicated in US studies (presumably due to differences in demographics and clinical practice) we believe that this study of US and Canadian women is a valuable contribution to the existing literature.

2. In the abstract, line 62, just say that the composite neonatal outcome did not occur in any of the normal PGIF pregnancies, "not 0%".

Response: This sentence has been removed from the Abstract.

3. Line 75, modify sentence to "iatrogenic preterm delivery".

Response: Done (line 88).

4. It is clear you mean to compare potential differences in findings when cases were classified according to 2013 definitions versus 2019 ACOG guidelines although your explanation in line 131 does not make sense nor does line 187 in the results section.

Response: Thank you for highlighting the need for clarification. The explanation in the Methods has been revised (lines 158-160): “In PETRA, maternal hypertensive disorder diagnoses were adjudicated using 2013 ACOG criteria. For the present analysis, these diagnoses were reclassified using 2019 ACOG recommendations and stratified according to PlGF level.” The sentence in the Results section (line 187 in the original submission) has been removed for clarity.

5. Line 137, I'm not sure that differentiating between gestational hypertension with severe range blood pressures and superimposed preeclampsia and preeclampsia with severe features is necessary or pertinent to the study.
Response: We thank the reviewer for this point and agree that the distinction between the various forms of severe preeclampsia may not be pertinent to our analysis. However, given the updated definitions in the 2019 ACOG Bulletin (Number 202: Gestational Hypertension and Preeclampsia) and the potential for confusion surrounding these definitions, we have kept these details in the Methods section to ensure that readers understand what we are referring to.

6. Similarly, in line 137, the sentence discussing the divisions of superimposed preeclampsia can be eliminated as it does not impact the study nor does it add to the manuscript.

Response: Agree. This sentence has been removed.

7. Line 221, the meaning of this sentence referencing shortened interval delivery is unclear.

Response: This has been revised (lines 263-267): “The primary PETRA analysis showed that PlGF is significantly correlated with time to delivery; the median time from enrollment to delivery was 45, 10, and 2 days for normal, low, and very low PlGF, respectively. Our analysis reveals the serious neonatal and maternal consequences of earlier delivery in the abnormal PlGF groups.”

8. Ultimately, the problem with this study is that it is still investigational and PIGF is not available clinically.

Response: We agree that the results of this analysis will not change clinical practice, as randomized trial data are needed. However, investigational studies like ours provide important evidence that serves as the basis for clinical trials. Indeed, similar studies in the UK preceded the recent randomized clinical trial of PIGF testing (Duhig et al, Lancet 2019, doi:10.1016/S0140-6736(18)33212-4), which led to the incorporation of PIGF into NICE guidelines for managing hypertension in pregnancy (Webster K, et al. BMJ 2019, DOI: 10.1136/bmj.l5119).

Reviewer #4:
The authors have conducted a secondary analysis of the PETRA Trial in an attempt to determine whether PIGF is associated with adverse neonatal and maternal outcomes in women with a suspected or confirmed diagnosis of preeclampsia.

1. This was a well-conducted study and the manuscript was well-written. While abnormally low PIGF was associated with composite adverse neonatal outcomes in the population of patients that were studied, the clinical implications are uncertain.

Response: Thank you. We agree that the clinical implications are uncertain (also see response to Reviewer 2, Point 2).

2. I don’t believe that this information is available, but I would be curious to see if there was correlation with low PIGF values and ultrasound abnormalities (e.g. abnormal umbilical artery Doppler, abnormal BPP, etc). Does a low PIGF in and of itself identify patients at higher risk for an adverse
neonatal or maternal outcome or is this seen in association with other parameters that may predict the same?

**Response:** We appreciate this excellent point and agree that the correlation between PlGF and ultrasound findings, such as Dopplers, would be very interesting and might reveal the added value of PlGF. However, this analysis is outside the scope of the current study as these details are not available. Interestingly, an observational study by Molarvec and colleagues that compared PlGF with Dopplers found that abnormal PlGF identified fetuses at risk for later adverse outcomes that were not identified by abnormal Dopplers (Molarvec et al., *BMC Pregnancy and Childbirth* 2013, doi:10.1186/1471-2393-13-161), suggesting that these tests are not redundant.

2. I agree that while the information gleaned from this study may be important and clinically valuable, use of PlGF as a clinical tool should be subjected to a randomized trial as the authors suggest to ascertain its true clinical utility.

**Response:** We agree and have stated this in the Discussion (lines 345-346): “randomized trials including U.S. women will be required to determine the value of PlGF as an adjunct to current management....”

3. I would like to know how the authors arrived at the cut offs for low (less than or equal to 100 pg/mL) and very low (< 12 pg/mL) PlGF values. This seems like an arbitrary definition.

**Response:** Please see response to Reviewer 2, Point 3 above.

**STATISTICAL EDITOR COMMENTS:**

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

Table 1: There are statistically significant differences in mean GA for the cohorts, but apparently there was no adjustment of PIGF level for GA.

**Response:** Please see response to Reviewer 2, Point 3 above.

Table 2: The aRR adjustment used 6 variables (lines 146-151), while the counts for adverse outcomes were 68 and 3 for the composite. This is an unfavorable ratio of variables used as adjustors vs the counts of adverse outcomes, which was also true for many of the other comparisons for Low PIGF. These are likely over fitted to the data. Similarly, for the very low PIGF, the counts were 58 and 13, still too few for precise adjustment.

**Response:** We appreciate this comment and agree that the number of adverse outcomes is low. The uncertainty regarding RR estimates is reflected in the width of the confidence intervals. Although the number of adverse outcome in our study is low, the rule of thumb is that one predictive variable can be studied for every 8-10 events. Since the total numbers for composite neonatal and maternal
adverse outcomes were 71 and 53, respectively, our regression analyses with 6 variables could still fit the data (need 48-60 events). We acknowledge that our results should be interpreted with caution and have added this caveat to the revised Discussion (lines 324-325): “Given the overall low number of adverse outcomes in our study, the adjusted results should be interpreted with caution.”

Table 3: Similar issue with aRRs and low counts (low PIGF had 7 and 46 counts of composite adverse), while very low PIGF had 34 and 19 for adverse composite events.

Response: Please see response above.

Although the use of RR and aRRs are useful, many of the aRRs in the study are based on insufficient counts and are not reliable estimates. Many readers would likely find expression of composite adverse events for Low or very low PIGF categories useful if expressed in terms of sensitivity and specificity, each with appropriate CIs.

Response: Thank you for this suggestion. Sensitivity and specificity with 95% CIs as well as positive and negative predictive values have been added (Appendix 3) and are discussed in the revised Results section (lines 243-248): “PIGF test characteristics are presented in Appendix 3. For the composite neonatal outcome, low PIGF had a sensitivity and specificity of 95.8% and 35.5%, respectively; sensitivity and specificity were 86.8% and 34.3%, respectively, for the composite maternal outcome. Using the very low cutoff decreased the sensitivity and increased the specificity of PIGF. Although the positive predictive value was poor, low PIGF had a high negative predictive value for neonatal (99.2%) and maternal outcomes (98.1%).”

We believe that relative risks are informative and of interest to physicians, therefore, these were retained in the revised manuscript.

ASSOCIATE EDITOR COMMENTS:

We feel that the clinical value of these data as presented would be subject to misinterpretation, specifically with reference to the adjusted risks.

To wit, if I understand correctly, using a threshold of 100, ~2/3 of patients would be classified as having a low value. And although they have an increased risk of the composite neonatal outcome, 90% of these "abnormal values" are not associated with the composite outcome.

Likewise, with the threshold of 12, still ~ 1/3 of patients would be considered to have an abnormal value, and of these women, >80% of these values are not associated with the adverse neonatal composite.

Response: Please see responses to Reviewer 1, Point 7, and Reviewer 2, Point 1 above.

So in your revision, please move away from relative risks and present data in terms of sensitivity and
specificity with 95% CIs.

Response: Thank you for this comment, which was expressed by other reviewers. Please see response to the last comment from the Statistical Editor above.

Thank you.

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.
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Response: OPT-IN

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   (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.
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were fully involved at all stages of publication and presentation development and are willing to take public responsibility for all aspects of the work.

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(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).

Response: Done. However, no funding was received for this study. The relevant information is listed under "Disclosures".

(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).


Response: This was added. However, no funding was received for this study. Including this section may give the false impression that the study was funded. If the Editors agree, we prefer to omit this entire section.

4. On your STROBE checklist, please indicate the page number where each item appears. You may write this in the margin of the checklist.

5. Standard obstetric and gynecology data definitions have been developed through the reVITALize...
initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology 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.

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