

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

Date: May 09, 2019
To: "Divya Mallampati" [REDACTED]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-19-738

RE: Manuscript Number ONG-19-738

A Cost-Effectiveness Analysis of Strategies for Prescribing Aspirin to Prevent Preeclampsia

Dear Dr. Mallampati:

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

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

Your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by May 30, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: Overall, this is a potentially important topic and of interest. It was a bit hard to follow exactly what the authors did in the Methods section and they did not report a specific cost-effectiveness ratio anywhere, so I couldn't figure out how such ratios were calculated. I have the following specific comments that I believe could improve the study:

1. Abstract: The cost-effectiveness threshold should be stated in the Abstract.
2. Abstract: It is commendable that the authors did a Monte Carlo simulation, but it appears that the universal approach was only preferred in 91% of simulations. This is not that different from a p-value of 0.09, so the findings should be tempered in the Conclusion to represent that (e.g. may prevent instead of prevents). I would suggest that the authors suggest that greater certainty is needed before recommending universal ASA.
3. Introduction: I think the framing around biomarker and other screening approaches is great and more frank information about this idea would help the reader. Why not state, such screening approaches really only benefit patients in developed countries if there is a way to prevent preeclampsia and the only intervention identified to date is ASA which is a LOT cheaper than the screening approaches and while nothing is riskless, the risks are quite low, it appears.
4. Methods: As noted above, a cost-effectiveness study's outcome is costs per outcomes. For an intervention to be considered incrementally cost effective, an a priori cost-effectiveness threshold should be identified. When the outcome is life years or quality-adjusted life years, usually \$50-100,000 per LY or QALY is used, but it less well defined with other outcomes. How did the authors intend for the C-E threshold to be defined?
5. Methods: The perspective of the study is not explicitly stated - was it societal?
6. Methods: The time frame for consideration is unclear, did the authors use lifetime outcomes for mothers and neonates?
7. Methods: The assumption was that ASA lowered the risk of preeclampsia similarly for high- and low-risk individuals?
8. Methods: How were costs discounted? What discount rate?
9. Methods: The assumption is that incremental analyses would occur, was that the case?
10. Methods: The authors mention a Monte Carlo simulation, what types of distributions were utilized? Again, how was C-E defined to ascertain the preferred strategies?

11. Results: The overall preeclampsia risk used in the model was 4.234%? It is a very specific number, is it based on a particularly epidemiologic study?
12. Results: In lines 162-168, was the assumption that fewer women in the universal approach took ASA, but all of the high-risk women identified by USPSTF did? Or did you vary the compliance rate for everyone in the same fashion? I ask, b/c it seems odd that the compliance would only go down for the universal group and not other groups.
13. Results: In general, it is usual to present the Results in past tense, the authors tended to use both past and also present tense.
14. Results: In the two-way SA, there is a willingness to pay of \$90K, where did this number come from?
15. Discussion: I think great to underscore that at this time biomarker screening does not seem to offer much benefit.
16. Discussion: Given that the authors don't appear to use LYs or QALYs as outcomes, there should be probably be something about comparability of their CEA thresholds to other clinical settings, depending on what they used.
17. Discussion: I think it is critical that the authors bring the uncertainty of their findings into the Discussion. To be only 91% certain regarding the preferred strategy does not really meet acceptable probability thresholds for making recommendations or stating that outcomes are different. If there was a clinical study that had a RR of 0.5 with a 95%CI of 0.2 to 1.1, we would call that not statistically significant even though the findings would be very suggestive. I think this finding of a 91% preferred strategy is similar and needs to be couched as such. It will be useful for the reader to understand this issue as the casual reader rarely understands the underpinnings of DA/CEA methodology and it is important to call out such issues.

Reviewer #2: This manuscript provides a cost-effectiveness analysis of various strategies of aspirin use (universal, USPSTF, ultrasound/biomarker, none) for pre-eclampsia prevention. This is particularly important in light of debate regarding more targeted identification of pre-eclampsia risk and aspirin use. The authors find that universal aspirin use is the dominant strategy for cost-effective prevention of pre-eclampsia.

The authors' efforts are to be commended. I have the following comments and points of clarification:

- 1) The abstract is concise and provides an appropriate assessment of findings. However, I found myself re-reading the sentences in the results section of the abstract, lines 39-43. The use of the words "yet" and "despite" is relatively confusing in this context, because one would expect that additional cases of pre-eclampsia would increase costs. However, the use of "yet" and "despite" lead the reader to believe that the next phrase will be unexpected, unusual, or counterintuitive. Please consider rephrasing these sentences for clarity.
- 2) The methods section overall provides the basic information needed to understand the inputs for the cost-effectiveness analysis. However, generally speaking, some additional granularity is needed to truly assess this work. While space is limited, I would recommend spending some considerable time to succinctly provide more detail in the methods section, or consider including an appendix or online supplementary material with the additional details requested below.
- 3) The four proposed strategies include no aspirin administration, biomarker and ultrasound measurements, USPSTF history-based risk stratification, and universal aspirin. However, it is this reviewer's understanding that the ASPRE trial and subsequent secondary analyses upon which the author's estimates of effect for biomarker and ultrasound studies are based actually utilized a combined marker of maternal history and ultrasound/biomarker measurements to derive the best detection rates. For instance, the 75% detection rate cited by the authors in the introduction (line 69-74) is derived from "...*combined* screening by maternal factors, uterine artery pulsatility index, mean arterial pressure, and placental growth factor" (O'Gorman et al 2016). It would be helpful for the authors to clarify in the text how this strategy for biomarker and serum screen is being operationalized in their model. In the decision tree, it appears that the first step in the ultrasound strategy is actually a positive vs negative USPSTF screening, which is then further subdivided into positive and negative serum/biomarker screenings, suggesting that this strategy is more accurately described as a combined or integrated screen based on history and serum/ultrasound markers. However, the text reads as though this strategy or scenario relies on serum/ultrasound markers alone. It may be that this is insignificant with regard to the ultimate results, but the text and the decision tree code should follow each other as closely as possible.
- 4) Given that the ASPRE studies did not initially stratify on USPSTF criteria, but rather included a host of maternal comorbidities and history (many of which appear on the USPSTF), how did the authors arrive at the estimation of the percentage of women with a positive USPSTF screen who would subsequently have a positive ultrasound screen? I have reviewed the cited literature and some related articles, and did not, based on an admittedly brief search, feel I could identify how the 54% rate of positive serum/ultrasound screen based on a positive USPSTF screen was derived (line 98-99).

- 5) A broader point regarding #4 is that, while the authors clearly have an excellent grasp of the literature in this field, the average reader may not be as well versed in the origins of each of the proposed point estimates, and, more importantly, ranges. A brief statement associated with the various proposed point estimates would be helpful. Werner et al have previously published a cost-effectiveness analysis on this subject that addresses this requirement adroitly, indicating the choices behind the ranges and improving the average reader's understanding of the data behind the choices in a succinct manner.
- 6) Recommend different phrasing of lines 106; I suggest "women eligible to receive aspirin must have one or more high-risk factors (...) or at least two-moderate risk factors (...)"
- 7) The willingness-to-pay threshold is somewhat vaguely described as double the estimated short-term maternal and neonatal cost of pre-eclampsia for 12mo after diagnosis (Stevens et al). This reviewer finds it challenging to understand this threshold for several reasons:
- it is unclear how this is related to the point estimates of cost for cases of pre-term and term pre-eclampsia (which are based on HCUP/AHRQ data) utilized for the analyses themselves (e.g., \$4410 + \$20604 for preterm preeclampsia). The study from which the willingness to pay threshold was derived also utilized HCUP data; I presume these differences are at least somewhat related to the fact that Stevens et al are describing costs over 12months, and the time over which pre-eclampsia costs are assessed is not described in this manuscript. It would help to clarify the time period over which the costs of preeclampsia are being assessed for this analysis (maternal delivery and neonatal admission to discharge costs only?)
 - In my experience, willingness-to-pay thresholds typically are derived from a societal (or health economics) values statement about willingness-to-pay for a certain outcome (e.g. a neonatal QALY, or a DALY). Some are based on surveys, others on governmental valuations of QALY as a function of GDP, etc; of course, these methods have their flaws, and reliance on QALY/DALY etc is problematic in many circumstances. In this area of inquiry, however, previously conducted cost analyses have utilized a QALY measure. This makes the choice of twice the short-term cost of preeclampsia seem arbitrary, and it is not clearly anchored to either the previous literature in this field or to healthcare economic choices or societal values statements. Because this analysis is conducted from a health care systems cost standpoint, identifying a cost threshold with some meaning for health systems will improve the analysis.
 - Previous cost analyses in this area have utilized neonatal QALY valued at 100,000 USD. It will be very difficult to compare this paper to others in the same field. These values have been well defined by previous cost analyses in this field and would improve the comparability of this study to others in the literature.
 - This reviewer also feels that the willingness to pay threshold seems high, especially from a health systems perspective (from which the rest of this study is conducted - Stevens et al's costs are derived from a combination of population/epidemiology and health care systems perspectives). The majority of deliveries affected by pre-eclampsia will take place at or near term, with costs on the lower end of the spectrum of overall costs. It seems relatively unlikely that a health system would entertain a willingness-to-pay nearly four times the average cost of preterm preeclampsia (~4,000 + ~20,000) to avoid one case of preeclampsia, nor is there any societal data on which to base this assumption.
- 8) Since universal aspirin was the dominant strategy in nearly all circumstances, I appreciate that the authors made the effort to determine those situations in which it was not the dominant strategy. However, it is relatively surprising to this reviewer to find a large portion of the results section devoted to the importance of adherence to/probability of having aspirin prescribed as the main factor which alters the dominance of the universal aspirin strategy. A careful reading of the model in the appendix shows that both the likelihood of getting aspirin and non-adherence are branches in the decision tree. However, the base case for adherence or probability of receiving aspirin is not described in the methods, nor are the studies upon which these base case assumptions would be based directly cited. This portion of the base case is also excluded from Table 1. Because of this, it is challenging to know how likely or unlikely it is that a 55% nonadherence to aspirin could represent a realistic situation. In contrast, the paragraphs detailing the sensitivity analyses for the side effects of aspirin clearly state how unlikely the rate of side effects would need to be in order to change the dominant strategy.
- 9) "Adherence" as described in the results appears to describe the probability that a patient receives aspirin which would encompass both provider compliance with guidelines for prescribing/recommending as well as with patient ability to obtain and take the medication. If the definition of adherence includes all of the above, it would be reasonable to describe briefly what is meant by or included in the "probability that a patient receives aspirin."
- 10) How do the authors assume that adherence/nonadherence is distributed both within the population of low risk/high risk women, and within each aspirin strategy? Given the relatively high frequency of missed opportunities for prevention with risk factor driven screening that the authors appropriately point out, are there any assumptions built into the model that alter whether adherence issues will be more or less of a factor in different strategies? It will be very important to clarify the assumptions behind probability of receiving aspirin within each strategy and across the population.
- 11) In general, this paper offers insights into cost effectiveness of various aspirin strategies. However, additional detail in the methods (greater detail and clarity regarding how point estimates and ranges were ascertained) as well as more clarity on the details of the base case, including for adherence probabilities, will greatly improve this study.

Reviewer #3: The authors present a decision analysis (cost-effectiveness analysis) of low-dose aspirin to prevent preeclampsia. The U.S. Preventive Services Task Force (USPSTF) recommendations, which are also in an ACOG CO from 2018, are compared with universal aspirin administration in pregnancy, with a strategy of serum analyte and uterine artery Doppler-based aspirin administration, and with a strategy of no aspirin. Comments and questions follow.

1. General comments.

a. No aspirin seems more like a control group than a viable strategy. Just something to consider.
 b. Looking over the 3 other strategies broadly, the USPSTF and analyte/ultrasound strategies seem similar to typical screening tests, i.e. goal of maximizing sensitivity but keeping the false positive rate low (like an ROC curve). Hence the 23.5% screen positive rate (percentage receiving aspirin if USPSTF guidelines are followed) in the authors' prior decision analysis. A model based on abnormal Doppler studies and analytes would be even more stringent. However, the universal strategy takes a different approach, 100% sensitivity with no concern about false positive rate. Under these assumptions, anything that requires a test cannot be as effective -- the universal strategy would have to lead to improved outcomes. Please address what it means to compare strategies that have different objectives.

2. Abstract. This is a faithful representation of the manuscript.

It might be helpful to include some assumptions in the methods (otherwise the reader has no way to figure out how the authors arrived at their findings). The conclusion states that the model holds "over a broad range of assumptions." Can you give the reader a better sense of what those were?

3. Introduction and Methods. Overall these sections are well written and reasonable.

A concern is lines 75-77 (and also lines 129-135). Respectfully, it is not realistic to consider that women across the United States might routinely receive testing for placental protein-13 for first trimester preeclampsia screening. It is similarly unlikely that physician offices might perform uterine artery PI screening in a large proportion of pregnancies (not recommended by ACOG, SMFM, or AIUM). Why is a model needed that incorporates an analyte not used in the United States and a Doppler study that is not routinely recommended? Suggest that the authors justify the inclusion of this strategy more fully.

4. Results. This section is also well written and clearly presented.

5. Discussion.

a. Lines 201-205. Please compare the assumptions and findings of the prior decision analysis (same authors) with the current one, considering the different results and different conclusion. I would think the change in position warrants at least a paragraph.
 b. Lines 224-225. ACOG CO 743 (2018) does not recommend use of aspirin to lower rates of fetal growth restriction or preterm birth. This is a topic that probably shouldn't be simply mentioned as a single sentence. Suggest referencing the CO.

Reviewer #4: This is a decision analysis model comparing strategies around aspirin for preeclampsia prevention, including biomarker/US measures. This is particularly relevant given existing conflicting inclusion with historical screening as well as utility of biomarker/US screening strategies. Though other studies have compared universal aspirin vs historical risk factor screening vs controls or other combos of these, and some of the same authors did a similar analysis parsing out the ACOG vs USPSTF recommendations--this is only study to include sonographic/biomarker screening methodologies.

Using decision analysis including Monte Carlo simulations, the favored strategy is a universal aspirin approach as providing superior preeclampsia reduction and cost-saving as long as usage is greater than 55-58% of pregnant women. This also carries a small increase in GI bleeding and respiratory complications.

Limitations include the multiple assumptions utilized for these simulations, some figures of which may change with time and geography (e.g. serum or sonographic testing costs). The authors acknowledge that some of the assumptions were also generated by European populations, so may not be generalizable to the US, and they do not address the controversies in timing of aspirin initiation or optimal dosing. Furthermore, the effect on medication adherence if aspirin was universally recommended would be interesting to evaluate as patient attitudes may significantly affect this.

Though the data supports a universal approach to aspirin prophylaxis, this does not necessarily reflect outcomes in a real-world scenario. Nonetheless, the authors provide a strong decision analysis to assist providers and/or systems in discussing policy and practice.

Reviewer #5:

1. This manuscript is a cost analysis comparing 4 methods of aspirin prophylaxis strategies for the prevention of preeclampsia. The four methods are 1) No aspirin, 2) Aspirin for patients who meet USPSTF criteria, 3) Aspirin for patients who meet ultrasound and serum screening criteria, 4) Universal aspirin. This analysis was performed using various health statistic registries and Tree Age 2018 software. The authors note that the point of the paper is to assess screening using biomarkers and ultrasound as compared to other screening strategies. Overall, universal aspirin strategy showed to prevent more cases of preeclampsia and cost the least amount of money of the 4 strategies.
2. The study question is novel. The authors address that similar questions have been evaluated (cost effectiveness of aspirin using different strategies. Reference #16), however this particular question is unique and applicable to patients in the US.
3. The methods of evaluation are appropriate for the question. The evaluation was thorough, using multiple registries and a validated decision analysis software. The methods are generalizable to many patient populations.
4. The study is very interesting and the findings are applicable to our daily practice. It supports the idea that universal aspirin administration can be beneficial.
5. The writing of the manuscript is clear, concise and is enjoyable to read. The order of information presented is organized and "tells a story." I did not note any spelling or grammatical errors. The length of the manuscript is appropriate.
 - a. The abstract clearly presents a summary of the study. A sentence addressing the ultrasound and biomarkers results could be added to the conclusions portion of the abstract.
 - b. The tables and figures are organized well and present pertinent information.
 - c. The references are relevant and appropriate.

STATISTICAL EDITOR COMMENTS:

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

lines 144-146: Why was the willingness-to-pay threshold set at 2x estimated cost of a case of preeclampsia, rather than 1x the cost or some round number such as \$50,000 or \$100,000. Also, the estimated short-term infant and maternal costs of pre-eclampsia would depend on the proportions of term vs pre-term pre-eclampsia (Table 1). The models have varying predictions for pre:term cases depending on the scenario of aspirin use. In other words, the average cost of infant and maternal care will depend on the case mix of preterm and term and not be the same for each scenario.

Table 1: Should include in Methods or as footnote to Table justification for how the ranges were determined. Could also be in supplemental.

Table 2: Should include as footnote or in title that each of these scenarios assume 100% compliance towards the respective scenarios. Suggest additional row entries for total and incremental costs, each indexed per woman.

EDITOR COMMENTS:

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

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

- Please consider use of causal language here. You have not done an intervention trial (although your assumptions are based on intervention trials) and so should be associative language. For example, universal aspirin administration is associated with fewer cases of preeclampsia, money savings.....etc.

- Not limited to US> you could just drop "in the united states"

- identifying populations at high-risk of preeclampsia
- you also are comparing to a strategy without screening--universal treatment. Your description of your purpose should include that.
- There are recommendations in the literature about different dosing strategies: 81 or 150 (in Europe) or 162mg in the US. Given that some studies suggest higher efficacy with the higher dose, and the likely increased complication rates with the higher dose, it would be important for you to state what dose ASA you are using for your analysis.
- what assumptions did you make about maternal use of the intervention?
- was associated with a decrease
- Does that include an assessment of maternal use of ASA under the USPTFS strategy? Certainly, not all of the risk-in patients under that strategy would actually take the ASA as prescribed.

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

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

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

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

4. All studies should follow the principles set forth in the Helsinki Declaration of 1975, as revised in 2013, and manuscripts should be approved by the necessary authority before submission. Applicable original research studies should be reviewed by an institutional review board (IRB) or ethics committee. This review should be documented in your cover letter as well in the Materials and Methods section, with an explanation if the study was considered exempt. If your research is based on a publicly available data set approved by your IRB for exemption, please provide documentation of this in your cover letter by submitting the URL of the IRB website outlining the exempt data sets or a letter from a representative of the IRB. In addition, insert a sentence in the Materials and Methods section stating that the study was approved or exempt from approval. In all cases, the complete name of the IRB should be provided in the manuscript.

5. Have Figure 1 or the Appendix figure been previously published in another source? If yes, please provide the original documents and submit permission letters from the copyright holders for print and electronic use.

Tables, figures, and supplemental digital content should be original. The use of borrowed material (eg, lengthy direct quotations, tables, figures, or videos) is discouraged, but should it be considered essential, written permission of the copyright holder must be obtained. Permission is also required for material that has been adapted or modified from another source. Both print and electronic (online) rights must be obtained from the holder of the copyright (often the publisher, not the author), and credit to the original source must be included in your manuscript. Many publishers now have online systems for submitting permissions request; please consult the publisher directly for more information.

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

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

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

In addition, the abstract length should follow journal guidelines. The word limits for different article types are as follows: 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. Line 204-5: We discourage claims of first reports since they are often difficult to prove. How do you know this is the first report? If this is based on a systematic search of the literature, that search should be described in the text (search engine, search terms, date range of search, and languages encompassed by the search). If on the other hand, it is not based on a systematic search but only on your level of awareness, it is not a claim we permit.

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

13. 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>.

14. Figure 1: When you submit your revision, art saved in a digital format should accompany it. If your figure was created in Microsoft Word, Microsoft Excel, or Microsoft PowerPoint formats, please submit your original source file. Image files should not be copied and pasted into Microsoft Word or Microsoft PowerPoint.

Appendix Figure: This figure will need to appear as online-only. It will not display well due to the size. Please name this as Appendix 1 throughout your submission.

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

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

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

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

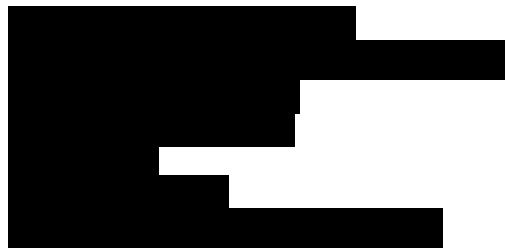
Again, your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by May 30, 2019, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Nancy C. Chescheir, MD
Editor-in-Chief

2017 IMPACT FACTOR: 4.982
2017 IMPACT FACTOR RANKING: 5th out of 82 ob/gyn journals

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May 29, 2019

Dear editors,

Thank you for your consideration of our manuscript titled, “A Cost-Effectiveness Analysis of Strategies for Prescribing Aspirin to Prevent Preeclampsia.” We greatly appreciate your feedback on this piece. We have revised our paper to both respond to feedback and reflect the changes requested by the reviewers. In the page following my signature are the comments and questions that were made in the original manuscript and our responses. All line references in the following responses correspond to the revised manuscript with tracked changes. We are submitting our manuscript with tracked changes as well as a clean copy.

Of note, we have agreed to publishing our response letter and subsequent email correspondence related to our manuscript.

We hope that we can continue working with you on the publication of this research and thank you again.

Sincerely, and on behalf of all the authors,



Divya Mallampati, MD, MPH
Department of Obstetrics and Gynecology
Northwestern University

Reviewer #1

1. Abstract: The cost-effectiveness threshold should be stated in the Abstract.

We have modified the abstract to include the willingness-to-pay threshold (Lines 41).

2. Abstract: It is commendable that the authors did a Monte Carlo simulation, but it appears that the universal approach was only preferred in 91% of simulations. This is not that different from a p-value of 0.09, so the findings should be tempered in the Conclusion to represent that (e.g. may prevent instead of prevents). I would suggest that the authors suggest that greater certainty is needed before recommending universal ASA.

We agree that a clinical recommendation to move towards universal aspirin requires greater certainty (among other considerations such as feasibility, equity, etc). While the purpose of this paper was not to arrive at such a conclusion or to make definitive recommendations regarding aspirin prophylaxis strategies, we have added a phrase in the Discussion to reflect that more model certainty is needed prior to identifying the best approach towards preeclampsia prophylaxis (Lines 289-291).

Moreover, our specific goal was to compare biomarker screening to other strategies of which we demonstrated in our Monte Carlo simulations that biomarker screening was cost-effective in 0% of simulations.

3. Introduction: I think the framing around biomarker and other screening approaches is great and more frank information about this idea would help the reader. Why not state, such screening approaches really only benefit patients in developed countries if there is a way to prevent preeclampsia and the only intervention identified to date is ASA which is a LOT cheaper than the screening approaches and while nothing is riskless, the risks are quite low, it appears.

While we have not added this analysis to the introduction given space constraints, we have added to the discussion in order to better clarify that universal aspirin, in comparison to other screening approaches, is low-cost intervention with few risks and significant clinical implications (Lines 281-283).

4. Methods: As noted above, a cost-effectiveness study's outcome is costs per outcomes. For an intervention to be considered incrementally cost effective, an a priori cost-effectiveness threshold should be identified. When the outcome is life years or quality-adjusted life years, usually \$50-100,000 per LY or QALY is used, but it less well defined with other outcomes. How did the authors intend for the C-E threshold to be defined?

We recognize that traditional cost-effectiveness analyses utilize LY or QALYs as outcomes yet we chose to define our outcome as the cost per case of preeclampsia. We chose this outcome primarily because we felt it was comparatively more clinically relevant than LY/QALYs. We have added to the discussion to reflect both the limitation of not using QALYs for this analysis and addressing this paper's comparability to prior literature (Lines 272-278).

As a result of this outcome, we defined our willingness-to-pay as two times the short term total cost (maternal and neonatal costs over 12 months) incurred due to one case of preeclampsia.

5. Methods: The perspective of the study is not explicitly stated - was it societal?

We have clarified the perspective of the study – societal – in the text of the manuscript (Line 153).

6. Methods: The time frame for consideration is unclear, did the authors use lifetime outcomes for mothers and neonates?

Given that outcome was only the number of preeclampsia cases, this analysis did not account for lifetime clinical outcomes of mothers or neonates. We clarified the model outcomes (Lines 179-180).

7. Methods: The assumption was that ASA lowered the risk of preeclampsia similarly for high- and low-risk individuals?

We did assume that the risk reduction of aspirin was the same for high and low risk individuals as there does not appear to be evidence suggesting that aspirin has a physiologically different effect on individuals who are high risk versus those who are low risk.

8. Methods: How were costs discounted? What discount rate?

We did not discount costs as this study was meant to interpret costs in a given year not over an extended time horizon.

9. Methods: The assumption is that incremental analyses would occur, was that the case?

We apologize but we did not understand this question.

10. Methods: The authors mention a Monte Carlo simulation, what types of distributions were utilized? Again, how was C-E defined to ascertain the preferred strategies?

Thank you for pointing this out. With the exception of the distributions for costs, the remaining model inputs (risk of preterm/term preeclampsia, probability of a positive USPSTF screen, risk reduction due to aspirin use, aspirin related side effects) were varied along a normal distribution. Cost inputs were varied along a beta or gamma distribution (Lines 187-189).

As above, our cost-effectiveness threshold was defined as twice the short term total maternal and neonatal costs of preeclampsia. We felt that this estimate would provide a liberal threshold with which we assess cost-effective strategies.

11. Results: The overall preeclampsia risk used in the model was 4.234%? It is a very specific number, is it based on a particularly epidemiologic study?

This number was not based upon a particular study but is a product of the individual estimates we used for term and preterm preeclampsia. This overall preeclampsia risk is, therefore, the result of the base case estimate for term and preterm preeclampsia which are based upon the following references: 1,2,17,18 and 42. We have added to our discussion regarding this point (Lines 236-238).

12. Results: In lines 162-168, was the assumption that fewer women in the universal approach took ASA, but all of the high-risk women identified by USPSTF did? Or did you vary the compliance rate for everyone in the same fashion? I ask, b/c it seems odd that the compliance would only go down for the universal group and not other groups.

Thank you for this question. In those lines (now Lines 202-208), we specifically assumed that the probability that women in the universal approach changed while all other high risk women (in the USPSTF arm) stayed at 100% aspirin initiation. We later performed two-way sensitivity analyses (Figure

1) which demonstrates how both variations in aspirin initiation with the universal approach and the other approaches shifts the most cost-effective strategy.

13. Results: In general, it is usual to present the Results in past tense, the authors tended to use both past and also present tense.

We have changed all tenses in the Results section to the past tense.

14. Results: In the two-way SA, there is a willingness to pay of \$90K, where did this number come from?

This estimate was derived from recent population-level data that estimated the short term maternal and neonatal costs of preeclampsia (Stevens et al., J Obstet Gynecol, 2017). We chose a willingness-to-pay threshold that was twice the value of the short term costs in order to ensure a liberal threshold for the analysis.

15. Discussion: I think great to underscore that at this time biomarker screening does not seem to offer much benefit.

We have noted this and have added additional phrasing to the Discussion (Lines 233-235).

16. Discussion: Given that the authors don't appear to use LYs or QALYs as outcomes, there should be probably be something about comparability of their CEA thresholds to other clinical settings, depending on what they used.

Please see response to #14.

17. Discussion: I think it is critical that the authors bring the uncertainty of their findings into the Discussion. To be only 91% certain regarding the preferred strategy does not really meet acceptable probability thresholds for making recommendations or stating that outcomes are different. If there was a clinical study that had a RR of 0.5 with a 95%CI of 0.2 to 1.1, we would call that not statistically significant even though the findings would be very suggestive. I think this finding of a 91% preferred strategy is similar and needs to be couched as such. It will be useful for the reader to understand this issue as the casual reader rarely understands the underpinnings of DA/CEA methodology and it is important to call out such issues.

We agree that our findings do not imply a definitive recommendation for the use of universal aspirin, and do not believe a cost-effective analysis would allow such a determination to be made. That said, we continue to believe that the model is relatively robust and points to the strategy that under widely varying assumptions remains the best from a cost-effective standpoint. The Monte Carlo results do not truly track to a p value, and should not be interpreted in a truly identical way, although do agree that the Monte Carlo analysis, like the p value, does not allow definitively dichotomous conclusions to be made (but does allow relative confidence in the conclusions, in the context of other information, to be made). We believe we have not conveyed definitive information and conveyed our level of uncertainty as well.

Reviewer #2:

1) The abstract is concise and provides an appropriate assessment of findings. However, I found myself re-reading the sentences in the results section of the abstract, lines 39-43. The use of the words "yet" and "despite" is relatively confusing in this context, because one would expect that additional cases of pre-eclampsia would increase costs. However, the use of "yet" and "despite" lead the reader to believe that the next phrase will be unexpected, unusual, or counterintuitive. Please consider rephrasing these sentences for clarity.

We appreciate this comment and have changed the results section of the abstract to be clearer.

2) The methods section overall provides the basic information needed to understand the inputs for the cost-effectiveness analysis. However, generally speaking, some additional granularity is needed to truly assess this work. While space is limited, I would recommend spending some considerable time to succinctly provide more detail in the methods section, or consider including an appendix or online supplementary material with the additional details requested below.

We appreciate the comment, although are not entirely clear what information is not granular enough. We believe that – within the constraints of a journal article – we have provided the information that is necessary to be able to make understand the approach. Certainly, if there is something specific that remains unclear, we would be happy to address it. Also, we hope the changes we have made have ameliorated some of this concern.

3) The four proposed strategies include no aspirin administration, biomarker and ultrasound measurements, USPSTF history-based risk stratification, and universal aspirin. However, it is this reviewer's understanding that the ASPRE trial and subsequent secondary analyses upon which the author's estimates of effect for biomarker and ultrasound studies are based actually utilized a combined marker of maternal history and ultrasound/biomarker measurements to derive the best detection rates. For instance, the 75% detection rate cited by the authors in the introduction (line 69-74) is derived from "...*combined* screening by maternal factors, uterine artery pulsatility index, mean arterial pressure, and placental growth factor" (O'Gorman et al 2016). It would be helpful for the authors to clarify in the text how this strategy for biomarker and serum screen is being operationalized in their model. In the decision tree, it appears that the first step in the ultrasound strategy is actually a positive vs negative USPSTF screening, which is then further subdivided into positive and negative serum/biomarker screenings, suggesting that this strategy is more accurately described as a combined or integrated screen based on history and serum/ultrasound markers. However, the text reads as though this strategy or scenario relies on serum/ultrasound markers alone. It may be that this is insignificant with regard to the ultimate results, but the text and the decision tree code should follow each other as closely as possible.

That particular design of our model was intentional and applied across all strategy arms (no aspirin, USPSTF, ultrasound/biomarker, and universal aspirin) in order to keep all inputs consistent. While it appears in the model schematic that the screening is done in a stepwise fashion as is suggested in this comment, relevant probabilities are then applied to each group depending on which strategy arm they are in. For example, to assess the outcome in the USPSTF strategy arm, individuals who have a positive USPSTF screen (but are either positive or negative by the biomarker/ultrasound strategy) are only given aspirin. In the biomarker/ultrasound screening arm, people who are negative by biomarker/ultrasound screening, regardless of their USPSTF screen, do NOT receive aspirin.

While the above was detailed in our methods, we have clarified this further in Lines 129-132.

4) Given that the ASPRE studies did not initially stratify on USPSTF criteria, but rather included a host of maternal comorbidities and history (many of which appear on the USPSTF), how did the authors arrive at the estimation of the percentage of women with a positive USPSTF screen who would subsequently have a positive ultrasound screen? I have reviewed the cited literature and some related articles, and did not, based on an admittedly brief search, feel I could identify how the 54% rate of positive serum/ultrasound screen based on a positive USPSTF screen was derived (line 98-99).

We agree that these estimations are hard to find and that they are not obvious from the cited literature. The estimations were derived from O’Gorman et al 2016 and confirmed with data from the ASPRE trial. The value of 54% comes to from the screen positive rate of preeclampsia for all pregnant women who had a prior history of preeclampsia (we wanted this estimation to reflect the average screen positive risk for a population that is known to be high risk). In the ASPRE studies, the screen positive rate of ultrasound/biomarker screening among women with a positive ACOG screen was 16% while it was 56% with women with a positive NICE screen. Ultimately, we chose to keep the average around 54-56%.

The maximum and minimum for this estimation is taken from subsets of high risk populations within that paper (White women with a prior history of preeclampsia, Afrocarribean women with preeclampsia, etc). When we ran one-way sensitivity analyses, we used the range reported in the paper (43-86%) (115-120). While not specifically reported in the paper, when we expand this range to 1-99% the model continues to demonstrate that universal aspirin is the dominant strategy.

5) A broader point regarding #4 is that, while the authors clearly have an excellent grasp of the literature in this field, the average reader may not be as well versed in the origins of each of the proposed point estimates, and, more importantly, ranges. A brief statement associated with the various proposed point estimates would be helpful. Werner et al have previously published a cost-effectiveness analysis on this subject that addresses this requirement adroitly, indicating the choices behind the ranges and improving the average reader's understanding of the data behind the choices in a succinct manner.

Thank you for your suggestion. We have added additional details to the Methods in order to clarify where our base-case estimates and ranges were derived. (Lines 115-120, 125-128, 136-140, 147-152).

6) Recommend different phrasing of lines 106; I suggest "women eligible to receive aspirin must have one or more high-risk factors (...) or at least two-moderate risk factors (...)"

We have modified this phrasing (Lines 133-136).

7) The willingness-to-pay threshold is somewhat vaguely described as double the estimated short-term maternal and neonatal cost of pre-eclampsia for 12mo after diagnosis (Stevens et al). This reviewer finds it challenging to understand this threshold for several reasons:

a. it is unclear how this is related to the point estimates of cost for cases of pre-term and term pre-eclampsia (which are based on HCUP/AHRQ data) utilized for the analyses themselves (e.g., \$4410 + \$20604 for preterm preeclampsia). The study from which the willingness to pay threshold was derived also utilized HCUP data; I presume these differences are at least somewhat related to the fact that Stevens et al are describing costs over 12months, and the time over which pre-eclampsia costs are assessed is not described in this manuscript. It would help to clarify the time period over which the costs of preeclampsia are being assessed for this analysis (maternal delivery and neonatal admission to discharge costs only?)

We agree that these differences in estimates are confusing. The immediate costs for term, preterm preeclampsia, and neonatal care are derived from HCUP data – this solely encompasses hospitalization costs (admission to discharge). What we use to define our willingness-to-pay threshold is derived from

data regarding short term health care costs for the mother and neonate for one case of preeclampsia are over the course of 12 months. In order to clarify both how we reached these estimations and how to interpret them, we have added to our methods to clarify the time scale of the cost used for the WTP threshold (Lines 161-163, Lines 180-183).

b. In my experience, willingness-to-pay thresholds typically are derived from a societal (or health economics) values statement about willingness-to-pay for a certain outcome (e.g. a neonatal QALY, or a DALY). Some are based on surveys, others on governmental valuations of QALY as a function of GDP, etc; of course, these methods have their flaws, and reliance on QALY/DALY etc is problematic in many circumstances. In this area of inquiry, however, previously conducted cost analyses have utilized a QALY measure. This makes the choice of twice the short-term cost of preeclampsia seem arbitrary, and it is not clearly anchored to either the previous literature in this field or to healthcare economic choices or societal values statements. Because this analysis is conducted from a health care systems cost standpoint, identifying a cost threshold with some meaning for health systems will improve the analysis.

We agree that QALYs are a common outcome for cost-effectiveness models. However, there are many downsides and challenges to the reliance on QALYs and thus cost-effective analyses often use specific outcomes as the measure of effect as we did in this case (cost averted or spent per case of preeclampsia). In order to clarify our intentions regarding our chosen clinical outcome, we have addressed this in the limitations section of the discussion (Lines 272-278).

c. Previous cost analyses in this area have utilized neonatal QALY valued at 100,000 USD. It will be very difficult to compare this paper to others in the same field. These values have been well defined by previous cost analyses in this field and would improve the comparability of this study to others in the literature.

The mix (as well as dearth) of literature in this area has utilized both neonatal QALYs (Werner et al 2015, Shmueli et al 2012) as well as costs needed to avert cases of preeclampsia (Shmueli et al 2012, Ortved et al 2019). Both metrics have merit in our opinion. We attempted to better explain our choice for this model and the associated WTP.

d. This reviewer also feels that the willingness to pay threshold seems high, especially from a health systems perspective (from which the rest of this study is conducted - Stevens et al's costs are derived from a combination of population/epidemiology and health care systems perspectives). The majority of deliveries affected by pre-eclampsia will take place at or near term, with costs on the lower end of the spectrum of overall costs. It seems relatively unlikely that a health system would entertain a willingness-to-pay nearly four times the average cost of preterm preeclampsia (~4,000 + ~20,000) to avoid one case of preeclampsia, nor is there any societal data on which to base this assumption.

Thank you for this comment. Willingness-to-pay thresholds, in general, are arbitrary as each person or population likely has a different amount they would pay to avoid a particular effect. While \$50 or \$100 K are common in OB literature, this is not an evidence based threshold. We chose a liberal threshold (twice the short terms costs of preeclampsia) in order to identify areas where the dominant or cost-effectiveness strategy might shift. However, we were careful to also report the cost per each case of pre-eclampsia per prevention strategy so the reader could compare strategies using other WTP thresholds.

8) Since universal aspirin was the dominant strategy in nearly all circumstances, I appreciate that the authors made the effort to determine those situations in which it was not the dominant strategy. However, it is relatively surprising to this reviewer to find a large portion of the results section devoted to the importance of adherence to/probability of having aspirin prescribed as the main factor which alters the dominance of the universal aspirin strategy. A careful reading of the model in the appendix shows that

both the likelihood of getting aspirin and non-adherence are branches in the decision tree. However, the base case for adherence or probability of receiving aspirin is not described in the methods, nor are the studies upon which these base case assumptions would be based directly cited. This portion of the base case is also excluded from Table 1. Because of this, it is challenging to know how likely or unlikely it is that a 55% nonadherence to aspirin could represent a realistic situation. In contrast, the paragraphs detailing the sensitivity analyses for the side effects of aspirin clearly state how unlikely the rate of side effects would need to be in order to change the dominant strategy.

We have tried to be clear in the results that we have not performed sensitivity analyses on our model with relation to "adherence" but rather the probability that a woman receives aspirin (regardless of strategy) (Lines 202-205). We have been careful not to make valuations regarding adherence because we did not have sufficient data to assess whether variations in true adherence by a patient would ultimately change her risk reduction of preeclampsia. With that said, we agree that our methods could have been clearer with regards to how we tested this particular probability and have added to our methods to elucidate this point (Lines 143-147).

9) "Adherence" as described in the results appears to describe the probability that a patient receives aspirin which would encompass both provider compliance with guidelines for prescribing/recommending as well as with patient ability to obtain and take the medication. If the definition of adherence includes all of the above, it would be reasonable to describe briefly what is meant by or included in the "probability that a patient receives aspirin."

Thank you, we appreciate this point. We have avoided using the term adherence in our paper to describe the probability that a woman receives aspirin in order to avoid confusion over its broad definition (as you have suggested above). We are careful to denote that our model and sensitivity analyses only account for the probability that women who need aspirin (either because they had a high risk screen or were in the universal aspirin arm) initiate it (Lines 143-147).

The only section in which we have addressed adherence as a general term is in the discussion in order to address arguments against universal aspirin suggesting that patients would not take a medication that was not specifically prescribed unless the patient was identified as high risk.

10) How do the authors assume that adherence/nonadherence is distributed both within the population of low risk/high risk women, and within each aspirin strategy? Given the relatively high frequency of missed opportunities for prevention with risk factor driven screening that the authors appropriately point out, are there any assumptions built into the model that alter whether adherence issues will be more or less of a factor in different strategies? It will be very important to clarify the assumptions behind probability of receiving aspirin within each strategy and across the population.

This is a great point. We do not specifically address adherence rates among those who get universal aspirin versus risk-based aspirin as we did not feel we had enough data to make conclusions about the risk reduction related to imperfect adherence. We have added additional lines in our methods to clarify that, in the base case, we assume 100% initiation of aspirin and perfect use (Lines 143-144).

11) In general, this paper offers insights into cost effectiveness of various aspirin strategies. However, additional detail in the methods (greater detail and clarity regarding how point estimates and ranges were ascertained) as well as more clarity on the details of the base case, including for adherence probabilities, will greatly improve this study.

Thank you for these comments. We agree that our methods needed further detail and hope that it has sufficient clarity. We will continue to identify adherence probabilities and their subsequent impact upon

aspirin in preeclampsia prevention which, as we noted before, are limited in this particular field or study.

Reviewer #3: The authors present a decision analysis (cost-effectiveness analysis) of low-dose aspirin to prevent preeclampsia. The U.S. Preventive Services Task Force (USPSTF) recommendations, which are also in an ACOG CO from 2018, are compared with universal aspirin administration in pregnancy, with a strategy of serum analyte and uterine artery Doppler-based aspirin administration, and with a strategy of no aspirin. Comments and questions follow.

1. General comments.

a. No aspirin seems more like a control group than a viable strategy. Just something to consider.

We agree that no aspirin is not a viable strategy and so did consider presenting this group as a control group. We felt, however, that the current presentation of the results, particularly with universal aspirin being a dominant strategy, was the easiest to understand from the perspective of the reader.

b. Looking over the 3 other strategies broadly, the USPSTF and analyte/ultrasound strategies seem similar to typical screening tests, i.e. goal of maximizing sensitivity but keeping the false positive rate low (like an ROC curve). Hence the 23.5% screen positive rate (percentage receiving aspirin if USPSTF guidelines are followed) in the authors' prior decision analysis. A model based on abnormal Doppler studies and analytes would be even more stringent. However, the universal strategy takes a different approach, 100% sensitivity with no concern about false positive rate. Under these assumptions, anything that requires a test cannot be as effective -- the universal strategy would have to lead to improved outcomes. Please address what it means to compare strategies that have different objectives.

This is a great point – while clearly universal aspirin use would avert the problem of both false negatives (and has no concerns regarding false positive rates) we feel that the downside is the potential unintended negative externalities (such as aspirin related side-effects) or that the strategy itself is not cost-effective. In order to clarify this point of differing objectives, we have added to our methods (Lines 101-104).

2. Abstract. This is a faithful representation of the manuscript.

It might be helpful to include some assumptions in the methods (otherwise the reader has no way to figure out how the authors arrived at their findings). The conclusion states that the model holds "over a broad range of assumptions." Can you give the reader a better sense of what those were?

We added to our abstract in order to give a sense of what our sensitivity analyses involved (Lines 41-45).

3. Introduction and Methods. Overall these sections are well written and reasonable.

A concern is lines 75-77 (and also lines 129-135). Respectfully, it is not realistic to consider that women across the United States might routinely receive testing for placental protein-13 for first trimester preeclampsia screening. It is similarly unlikely that physician offices might perform uterine artery PI screening in a large proportion of pregnancies (not recommended by ACOG, SMFM, or AIUM). Why is a model needed that incorporates an analyte not used in the United States and a Doppler study that is not routinely recommended? Suggest that the authors justify the inclusion of this strategy more fully.

We appreciate your perspective, but as FIGO and other professional societies begin to recommend first trimester ultrasound and analyte assessment, we felt assessing the cost implications of such a strategy in the US was important. We performed this analysis explicitly because this is not standard of care in the United States and because, with the exception of a few centers piloting these methods, physicians are not offering this screen. However, because it is a growing area of research that is being propagated in high resource settings (much like the US) we wanted to test the implementation of this screening modality in the United States (Lines 78-80).

4. Results. This section is also well written and clearly presented.

5. Discussion.

a. Lines 201-205. Please compare the assumptions and findings of the prior decision analysis (same authors) with the current one, considering the different results and different conclusion. I would think the change in position warrants at least a paragraph.

We have added to our discussion to compare the differences of these two analyses more substantially (Lines 249-257).

b. Lines 224-225. ACOG CO 743 (2018) does not recommend use of aspirin to lower rates of fetal growth restriction or preterm birth. This is a topic that probably shouldn't be simply mentioned as a single sentence. Suggest referencing the CO.

We have clarified this statement (Lines 286-288).

Reviewer #4: This is a decision analysis model comparing strategies around aspirin for preeclampsia prevention, including biomarker/US measures. This is particularly relevant given existing conflicting inclusion with historical screening as well as utility of biomarker/US screening strategies. Though other studies have compared universal aspirin vs historical risk factor screening vs controls or other combos of these, and some of the same authors did a similar analysis parsing out the ACOG vs USPSTF recommendations--this is only study to include sonographic/biomarker screening methodologies.

Using decision analysis including Monte Carlo simulations, the favored strategy is a universal aspirin approach as providing superior preeclampsia reduction and cost-saving as long as usage is greater than 55-58% of pregnant women. This also carries a small increase in GI bleeding and respiratory complications.

Limitations include the multiple assumptions utilized for these simulations, some figures of which may change with time and geography (e.g. serum or sonographic testing costs). The authors acknowledge that some of the assumptions were also generated by European populations, so may not be generalizable to the US, and they do not address the controversies in timing of aspirin initiation or optimal dosing. Furthermore, the effect on medication adherence if aspirin was universally recommended would be interesting to evaluate as patient attitudes may significantly affect this.

Though the data supports a universal approach to aspirin prophylaxis, this does not necessarily reflect outcomes in a real-world scenario. Nonetheless, the authors provide a strong decision analysis to assist providers and/or systems in discussing policy and practice.

Thank you for this feedback.

Reviewer #5:

1. This manuscript is a cost analysis comparing 4 methods of aspirin prophylaxis strategies for the prevention of preeclampsia. The four methods are 1) No aspirin, 2) Aspirin for patients who meet USPSTF criteria, 3) Aspirin for patients who meet ultrasound and serum screening criteria, 4) Universal aspirin. This analysis was performed using various health statistic registries and Tree Age 2018 software. The authors note that the point of the paper is to assess screening using biomarkers and ultrasound as compared to other screening strategies. Overall, universal aspirin strategy showed to prevent more cases of preeclampsia and cost the least amount of money of the 4 strategies.
2. The study question is novel. The authors address that similar questions have been evaluated (cost effectiveness of aspirin using different strategies. Reference #16), however this particular question is unique and applicable to patients in the US.
3. The methods of evaluation are appropriate for the question. The evaluation was thorough, using multiple registries and a validated decision analysis software. The methods are generalizable to many patient populations.
4. The study is very interesting and the findings are applicable to our daily practice. It supports the idea that universal aspirin administration can be beneficial.
5. The writing of the manuscript is clear, concise and is enjoyable to read. The order of information presented is organized and "tells a story." I did not note any spelling or grammatical errors. The length of the manuscript is appropriate.
 - a. The abstract clearly presents a summary of the study. A sentence addressing the ultrasound and biomarkers results could be added to the conclusions portion of the abstract.
 - b. The tables and figures are organized well and present pertinent information.
 - c. The references are relevant and appropriate.

Thank you for this feedback.

STATISTICAL EDITOR COMMENTS:

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

lines 144-146: Why was the willingness-to-pay threshold set at 2x estimated cost of a case of preeclampsia, rather than 1x the cost or some round number such as \$50,000 or \$100,000. Also, the estimated short-term infant and maternal costs of pre-eclampsia would depend on the proportions of term vs pre-term pre-eclampsia (Table 1). The models have varying predictions for pre:term cases depending on the scenario of aspirin use. In other words, the average cost of infant and maternal care will depend on the case mix of preterm and term and not be the same for each scenario.

We appreciate this point. To some degree all willingness-to-pay thresholds are arbitrary. The \$50-100K WTP that is often used is loosely linked to the cost of dialysis. Given the lack of data that informs most willingness to pay, we tried to be thoughtful in our threshold. As preeclampsia has more than just immediate costs, we chose to double the short term (12 month) systemic neonatal and maternal costs per 1 case of preeclampsia. While this threshold is not grounded in particular policy guidelines, we felt this threshold would be liberal enough to identify where cost-effective/dominant strategies shifted. We were careful to provide the cost to prevent a case of preeclampsia in each strategy so that the reader could compare strategies using other willingness to pay thresholds.

Table 1: Should include in Methods or as footnote to Table justification for how the ranges were determined. Could also be in supplemental.

We have added to our Methods section to outline from where and how ranges were identified.

Table 2: Should include as footnote or in title that each of these scenarios assume 100% compliance towards the respective scenarios. Suggest additional row entries for total and incremental costs, each indexed per woman.

We have added a comment to our Methods section regarding our assumptions on both compliance and aspirin initiation (Lines 141-147).

EDITOR COMMENTS:

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

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

- Please consider use of causal language here. You have not done an intervention trial (although your assumptions are based on intervention trials) and so should be associative language. For example, universal aspirin administration is associated with fewer cases of preeclampsia, money savings.....etc.

We have edited our abstract and several other parts of the manuscript in order to avoid the use of causal language.

- Not limited to US> you could just drop "in the united states'

Thank you. This change has been made to the manuscript.

- identifying populations at high-risk of preeclampsia

This change has been made to the manuscript.

- you also are comparing to a strategy without screening--universal treatment. Your description of your purpose should include that.

We have changed the description of our purpose to reflect that this analysis is comparing the cost-effectiveness of various aspirin administration strategies with respect to risk based screening, universal administration and no use.

- There are recommendations in the literature about different dosing strategies:81 or 150 (n Europe) or 162mg in the US. Given that some studies suggest higher efficacy with the higher dose, and the likely increased complication rates with the higher dose, it would be important for your to state what dose ASA you are using for your analysis.

In our analysis, we did not assume a particular dosing of aspirin and have included this assumption in the Methods (Line 143).

- what assumptions did you make about maternal use of the intervention?

We have clarified our assumptions about maternal use of aspirin in the Methods per your and other reviewers' request (Lines 141-147). Our specific assumptions were:

- 1.) That women initiated aspirin prior to 16 weeks of gestation*
- 2.) That there was 100% compliance or perfect use*
- 3.) That all women who were recommended to start aspirin, initiated it.*

- was associated with a decrease

- Does that include an assessment of maternal use of ASA under the USPTFS strategy? Certainly, not all of the risk-in patients under that strategy would actually take the ASA as prescribed.

That particular paragraph in the results only varies the probability that women in the universal aspirin arm receive aspirin. What is reported in that last sentence assumes that the USPSTF strategy has 100% initiation of aspirin. Figure 1 is used to illustrate how the probability of initiation of aspirin in universal administration is related to variations in the probability of initiation in the USPSTF strategy, our only two-way sensitivity analysis that demonstrated a shift in the preferred strategy. For example, if the probability of universal aspirin administration is less than 30%, the probability of aspirin administration in the USPSTF arm needs to be greater than 50% in order for it to be the preferred strategy.

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

A. OPT-IN: Yes, please publish my response letter and subsequent email correspondence related to author queries.

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

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

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

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