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: Aug 06, 2020
To: "Isabelle Chatroux" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-20-1531

RE: Manuscript Number ONG-20-1531

Herpes Simplex Virus Serotyping in Pregnant Women with a History of Genital Herpes: A Cost-Effectiveness Analysis

Dear Dr. Chatroux:

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).

Due to the COVID-19 pandemic, your paper will be maintained in active status for 30 days from the date of this letter. If we have not heard from you by Sep 05, 2020, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1:

This cost-effectiveness analysis focuses on the utility of sending HSV serology in patients with a history of genital herpes who have an outbreak in the third trimester. The main reasoning behind this evaluation is that while universal HSV screening in pregnancy has not been found to be cost-effective, evaluating serology in patients with an active outbreak in the third trimester may be useful as it could identify patients with a first episode non-primary infection, which has a much higher risk of vertical transmission, from those with a recurrent infection. The manuscript is generally easy to follow and includes most items on the CHEERS checklist for reporting economic evaluations. A strength of the study is the robustness of the dominant screening strategy even with the wide range of inputs evaluated on sensitivity analysis.

1) For probabilities of lesions at delivery or shedding at delivery (lines 150-158) authors may also consider the RCT by Watts et al. published AJOG 2003; 188:836-43 which reported the percentage of patients having lesions at the time of delivery while on acyclovir.

2) Consider updating estimates for costs in Table 2. For example, the cost of managing neonatal HSV disease is based on a 1996 cost-effectiveness analysis, which was estimated from a proportion of charges of caring for 132 herpes-infected neonates at UCSF. Similarly, estimates for the cost of delivery (Cesarean or vaginal) are based on publications from 2003 and 2005, respectively. Consider using larger national databases (MEPS, HCUP) which may have more nationally representative, modern data.

3) Please specify time horizon for this study - appears to be a lifetime horizon.

4) Outcomes are discounted but costs are not - please explain this choice.

5) Consider adding costs associated with a false positive HSV1 or HSV2 serology screening.

6) Lines 136-139: Check that this is the correct reference, currently refers to ACOG practice bulletin

7) Line 185: utility of neonatal death of 0.92, obtained from Thung and Grobman's AJOG 2005 cost-effectiveness analysis. Doublecheck this is the correct reference as I was unable to find any utility assigned a value of 0.92 in this manuscript.

Reviewer #2:

This manuscript describes a decision-analysis model of of the cost effectiveness of the value of serotyping women with a history of genital HSV and an outbreak during the third trimester of pregnancy. Using a variety of assumptions that are reasonable based on existing literature, the authors conclude that it is reasonable to perform serotyping this situation due to apparent improved outcomes and reduced aggregate costs. This topic is relatively important due to a lack of literature guidance of when serology has value during late pregnancy outbreak of genital HSV. While a decision model for cost effectiveness can provide valuable insight to guide management, the model is dependent on the underlying assumptions. Therefore, the validity of the model should be tested prospectively before widespread implementation if feasible using predefined primary and secondary outcomes of cost and effectiveness.

Additional comments:

1) Abstract:
a. The first sentence of the Methods is a bit confusing. It is not clear what is meant by "..., an estimate of the number of women in the United States with a history of genital HSY..." in the context of the rest of the sentence. Perhaps this should be in parentheses if it refers to the cohort of 100,000 women?
b. Addressing comments below also may lead to abstract revisions.

2) Introduction:
a. Page 6, line 92: It is not clear what is meant by "less conservatively." This should be rephrased to clarify what specifically the treatment approach might be.
b. The last paragraph seems to want to focus on the use of serology to help sort out first episode non-primary HSV infections. Would this group of women be expected to actually have a history of genital HSV? If not, then the purpose of the analysis is not really to focus on women with a positive HSV history. This should be clarified throughout the manuscript. Similarly, the title of the manuscript does not refer to the third trimester and should be adjusted if women with first episode non-primary infections do not have a clinical history of HSV.
c. Line 101: Consider replacing the words "...is cost effective" with "...could be cost effective" since the cost effectiveness determination can vary based on the various assumptions of the model used.

3) Materials and Methods:
a. Lines 116-125: It appears that the women described in this paragraph had no history of genital HSV, which is somewhat incongruous with the previously stated goal of analyzing the cost effectiveness of serology in women with an outbreak during pregnancy and a history of HSV.
b. How was the cost of the serology testing assigned and does it account for potential increased laboratory personnel/infrastructure needed to perform the additional tests.
c. Was there a sensitivity analyses performed based on how quickly the turn-around would be for serology, especially for those with an outbreak around delivery?
d. Line 183: What other conditions were used as a substitute for the utility estimates.

4) Results:
a. Provide the number of additional serology tests that would be performed with the strategy of testing.
b. Tables: Headings should be more descriptive.
c. Table 1: Define the column heading value in the legend
d. Table 3: Include in the column headings (N)
e. Figure 1: The resolution of this image is poor and the words could not be interpreted.
f. Figure 2: The legend does not completely describe how to interpret 2 sides of the figure.
g. Figure 3: Spell out WTP in the legend

5) Comments:
a. Would it be possible to use an estimated number of actual patients, rather than using a theoretic cohort of 100,000?

Reviewer #3:

INTRODUCTION

In line 96 on page 6, you use the phrase "higher risk of vertical transmission." Higher than what? I think you mean, "higher than women with recurrent infection."

DISCUSSION

Are you able to provide some estimate of how commonly serologic testing is used today in the specific framework you

describe? Are the majority of pediatric units compliant with your "immediate treatment" recommendations for infants born to mothers with "initial, non-primary infection?"

I think your argument makes great sense, and, in fact, you convinced me that this protocol should be adopted provided that the pediatricians consistently modify their treatment based on the results of the serology.

STATISTICAL EDITOR COMMENTS:

lines 140-141: The study referenced included ~ 58K pregnant women, not ~ 583K and the numbers with HSV shedding and subsequent infected neonates were much less.

As the Authors note (lines 142-145), the samples related to probability estimates were actually small and one example that did not result in transmission cannot be generalized to zero risk of transmission. Should develop in more detail the risk estimates and their ranges, which could be in supplemental material. But these probabilities (and ranges) seem at least as crucial as the probability of successful empiric antiviral treatment. Also need to justify the use of beta distribution for the probability estimates, particularly since some were based on small samples and a more liberal range might be justified.

lines 206-207: Should show the tornado analysis (could be in supplemental material) to show all the variables affected sensitivity analyses.

EDITOR'S COMMENTS:

Thank you for submitting your work to the Green Journal.

1) You state that there are ~1,500 neonatal infections a year in the United States. Do almost ~1,200 of them really arise (as you have modeled) from the 100,000 women with a history of herpes and active lesions in the third trimester? This seems too high a proportion. Are there data on this?

2) Please from the Title on make clear that it is women with both a history and active lesions in the third trimester that you are studying;

3) Please make sure your model's approach to cesarean comports with ACOG's updated approach

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. Obstetrics & Gynecology uses an "electronic Copyright Transfer Agreement" (eCTA). 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. If your study is based on data obtained from the National Center for Health Statistics, please review the Data Use Agreement (DUA) for Vital Statistics Data Files that you or one of your coauthors signed. If your manuscript is accepted for publication and it is subsequently found to have violated any of the terms of the DUA, the journal will retract your article. The National Center for Health Statistics may also terminate your access to any future vital statistics data.

4. Tables, figures, and supplemental digital content should be original. The use of borrowed material (eg, lengthy direct quotations, tables, figures, or videos) is discouraged. If the material is essential, written permission of the copyright holder must be obtained.

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. Permission is also required for material that has been adapted or modified from another source. Increasingly, publishers will not grant permission for modification of their material. Creative Commons licenses and open access have also made obtaining permissions more challenging. In order to avoid publication delays, we strongly encourage authors to link or reference to the material they want to highlight instead of trying to get permission to reprint it. For example, "see Table 1 in Smith et al" (and insert reference number). For articles that the journal invites, such as the Clinical Expert Series, the journal staff does not seek permission for modifications of material — the material will be reprinted in its original form.

When you submit your revised manuscript, please upload 1) the permissions license and 2) a copy of the original source from which the material was reprinted, adapted, or modified (eg, scan of book page(s), PDF of journal article, etc.).

If the figure or table you want to reprint can be easily found on the internet from a reputable source, we recommend providing a link to the source in your text instead of trying to reprint it in your manuscript.

5. Responsible reporting of research studies, which includes a complete, transparent, accurate and timely account of what was done and what was found during a research study, is an integral part of good research and publication practice and not an optional extra. Obstetrics & Gynecology supports initiatives aimed at improving the reporting of health research, and we ask authors to follow specific guidelines for reporting observational studies (ie, STROBE), observational studies using ICD-10 data (ie, RECORD), or meta-analyses and systematic reviews of observational studies (ie, MOOSE). Include the appropriate checklist for your manuscript type upon submission. Please write or insert the page numbers where each item appears in the margin of the checklist. Further information and links to the checklists are available at http://ong.editorialmanager.com. In your cover letter, be sure to indicate that you have followed the CONSORT, MOOSE, PRISMA, PRISMA for harms, STARD, STROBE, RECORD, CHEERS, SQUIRE 2.0, or CHERRIES guidelines, as appropriate.

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 data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-obstetrics-data-definitions and the gynecology data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-gynecology-data-definitions. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

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. 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).

9. 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 limit for Original Research articles is 300 words. Please provide a word count.

10. 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.

11. 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.

12. ACOG is moving toward discontinuing the use of "provider." Please replace "provider" throughout your paper with either a specific term that defines the group to which are referring (for example, "physicians," "nurses," etc.), or use "health care professional" if a specific term is not applicable.

13. 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%").

14. 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.

15. 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 at the Clinical Guidance page at https://www.acog.org/clinical (click on "Clinical Guidance" at the top).

16. Figure 1: This will likely be difficult to fit in print. Please consider moving to supplemental digital content.

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

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

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

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

Art that is low resolution, digitized, adapted from slides, or downloaded from the Internet may not reproduce.

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

appendixes should be added to a separate References list in the appendixes file.

18. Authors whose manuscripts have been accepted for publication have the option to pay an article processing charge and publish open access. With this choice, articles are made freely available online immediately upon publication. An information sheet is available at http://links.lww.com/LWW-ES/A48. The cost for publishing an article as open access can be found at https://wkauthorservices.editage.com/open-access/hybrid.html.

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.

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

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

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

Again, your paper will be maintained in active status for 30 days from the date of this letter. If we have not heard from you by Sep 05, 2020, we will assume you wish to withdraw the manuscript from further consideration..

Sincerely,

Dwight J. Rouse, MD
Associate Editor, Obstetrics

2019 IMPACT FACTOR: 5.524
2019 IMPACT FACTOR RANKING: 6th out of 82 ob/gyn journals

_____

Sept 12th, 2020

Dear Editors:

On behalf of my co-authors and myself, I am writing to submit our revised manuscript entitled, "Herpes Simplex Virus Serotyping in Pregnant Women with a History of Genital Herpes and an Outbreak in the Third Trimester of Pregnancy: A Cost-Effectiveness Analysis," for consideration as a published article in *Obstetrics & Gynecology*. Each author participated actively in the analyses, writing and editing of the manuscript, as well as approving this submitted version. None of the authors have financial or other conflicts of interest to disclose.

We designed a decision-analytic model to assess a theoretical cohort of women in the United States that have a history of genital herpes virus infection and an outbreak during the third trimester of pregnancy. This study involved no human subjects and was exempt from Institutional Review Board approval. This manuscript has not been previously published or submitted to another journal for publication.

This was presented as a poster presentation at the Society of Maternal Fetal Medicine Annual Meeting, 2020.

The lead author* affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.
Signed by: Isabelle Chatroux
*The manuscript's guarantor.

We have attached to this letter the reviewers' and editor's comments with our responses and revisions. If you have any further questions or comments, I will be serving as the corresponding author. Thank you for your consideration.

Sincerely,

Isabelle C. Chatroux
M.D. Candidate
University of Colorado School of Medicine
[redacted]

REVIEWER COMMENTS:

Reviewer #1:

This cost-effectiveness analysis focuses on the utility of sending HSV serology in patients with a history of genital herpes who have an outbreak in the third trimester. The main reasoning behind this evaluation is that while universal HSV screening in pregnancy has not been found to be cost-effective, evaluating serology in patients with an active outbreak in the third trimester may be useful as it could identify patients with a first episode non-primary infection, which has a much higher risk of vertical transmission, from those with a recurrent infection. The manuscript is generally easy to follow and includes most items on the CHEERS checklist for reporting economic evaluations. A strength of the study is the robustness of the dominant screening strategy even with the wide range of inputs evaluated on sensitivity analysis.

1) For probabilities of lesions at delivery or shedding at delivery (lines 150-158) authors may also consider the RCT by Watts et al. published AJOG 2003; 188:836-43 which reported the percentage of patients having lesions at the time of delivery while on acyclovir.

Thank you for bringing this article to our attention. The challenge we came across in finding probabilities of shedding and lesions at delivery was the particular population we were studying. Specifically, our group of interest is women who have an outbreak during the third trimester of pregnancy, so we already know they will have lesions and shed at some point during that time period. We chose to use the article cited to get an average length that either recurrent or first episode non-primary lesions are present for (9.3 days and 15 days, respectively) and divided it by the number of days in the third trimester to get the probability of lesions being present at delivery. We used a similar approach for shedding. Please let us know however, if you feel that this is insufficient, and we will re-evaluate other options.

2) Consider updating estimates for costs in Table 2. For example, the cost of managing neonatal HSV disease is based on a 1996 cost-effectiveness analysis, which was estimated from a proportion of charges of caring for 132 herpes-infected neonates at UCSF. Similarly, estimates for the cost of delivery (Cesarean or vaginal) are based on publications from 2003 and 2005, respectively. Consider using larger national databases (MEPS, HCUP) which may have more nationally representative, modern data.

Thank you for pointing this out, it is very challenging to find updated information on costs, so the usual approach is to inflate them over time using the medical component of the CPI. Data from HCUP, adjusted for neonatal HSV in the 2019 article by Donde et. al *Trends in the incidence, mortality, and cost of neonatal herpes simplex virus hospitalizations in the United States from 2003 to 2014* estimate an average of $27,843 for neonatal hospitalization for HSV alone. This adjusted to 2019 dollars would be approximately $27,843 x 1.175 = $32,716. However, this cost is all comers. Our current input for HSV hospitalization is $21,843. This estimates the costs of a short-term hospital stay that is representative of mild HSV, which only accrues costs of the current admission and no further sequelae. For

moderate and severe neonatal HSV, other costs need to be taken into consideration, including future doctor appointments and morbidities associated with the disease, so use of estimates based on a different severities of neurological impairment are used. Thus, we left our original cost estimate as we think it best reflects the cost of differing levels of HSV disease, but would be happy to consider the change. Of note, as our result was cost effective, the higher cost estimate would only make our primary results of serologic screening more robust.

Additionally, at the reviewer's suggestion, we have updated the cost of vaginal delivery and cesarean delivery to 2019 estimates from a recent publication by Hersh et. al *Maternal and Neonatal Hospitalization Costs Associated with Elective Induction of Labor at Term in California, 2007–2011.* These updated values did not change our findings in difference of cost and effectiveness.

3) Please specify time horizon for this study - appears to be a lifetime horizon.

Thank you for pointing this out. We did use a lifetime horizon and we have now clarified this in the Methods section at line #197.

4) Outcomes are discounted but costs are not - please explain this choice.

Thank you for this comment. All costs and QALYs were discounted. Costs that occur one time at the beginning of the model are not discounted per se, or the time they are discounted is 0. For QALYs, only those that occur annually were discounted at a rate of 3% per year. We have added further explanation of this to the methods section at line #169-170.

5) Consider adding costs associated with a false positive HSV1 or HSV2 serology screening.

Thank you for this comment. As our population all have a clinical history of genital HSV lesions, we don't believe that there would be false positive results, per se. While it is true that there can be a small amount of cross reactivity of such testing, given the clinical history, we are assuming that this population would have serologic positivity for either HSV1 or HSV2. The larger concern was that there could be false negatives which would lead to downstream costs of unnecessary neonatal treatment and we have included such costs in our model.

6) Lines 136-139: Check that this is the correct reference, currently refers to ACOG practice bulletin

Thank you for catching this. The first one is Bernstein et. al, the second one is ACOG practice bulletin, so we have made the appropriate change.

7) Line 185: utility of neonatal death of 0.92, obtained from Thung and Grobman's AJOG 2005 cost-effectiveness analysis. Doublecheck this is the correct reference as I was unable to find any utility assigned a value of 0.92 in this manuscript.

Thank you for pointing this out. The correct reference in Kupperman, 2000 and we have updated the manuscript with this information on lines #188-191. Additionally, we went through our references again to ensure that they were appropriately matched.

Reviewer #2:

This manuscript describes a decision-analysis model of the cost effectiveness of the value of serotyping women with a history of genital HSV and an outbreak during the third trimester of pregnancy. Using a variety of assumptions that are reasonable based on existing literature, the authors conclude that it is reasonable to perform serotyping this situation due to apparent improved outcomes and reduced aggregate costs. This topic is relatively important due to a lack of literature guidance of when serology has value during late pregnancy outbreak of genital HSV. While a decision model for cost effectiveness can provide valuable insight to guide management, the model is dependent on the underlying assumptions. Therefore, the validity of the model should be tested prospectively before widespread implementation if feasible using predefined primary and secondary outcomes of cost and effectiveness.

Thank you for this comment. We agree that this is an important issue with limited data and guidance. Further, we agree that applying the findings from decision analytic models should not happen broadly, but first with further prospective clinical research studies to validate the findings. However, individual clinicians may use these findings to guide care if they so choose.

Additional comments:

1) Abstract:
a. The first sentence of the Methods is a bit confusing. It is not clear what is meant by "..., an estimate of the number of women in the United States with a history of genital HSY..." in the context of the rest of the sentence. Perhaps this should be in parentheses if it refers to the cohort of 100,000 women?

Thank you for pointing this out. We have added parentheses for clarification.

Old text: We designed a decision-analytic model using TreeAge Pro software to assess an approach of routine HSV serotyping in a theoretical cohort of 100,000 women, an estimate of the number of women in the United States with a history of genital HSV and an outbreak during the third trimester of pregnancy.

New text: We designed a decision-analytic model using TreeAge Pro software to assess an approach of routine HSV serotyping in a theoretical cohort of 63,582 women (an estimate of the number of women in the United States with a history of genital HSV and an outbreak during the third trimester of pregnancy).

b. Addressing comments below also may lead to abstract revisions.

Thank you for pointing this out. We have made sure to review our abstract for consistency with the manuscript.

2) Introduction:
a. Page 6, line 92: It is not clear what is meant by "less conservatively." This should be rephrased to clarify what specifically the treatment approach might be.

Thank you for this comment. We have changed the sentence to eliminate "less conservatively", as this situation is not specified in guidelines and would therefore be up to the pediatricians discrepancy to decide if the neonate should be treated the same as a neonate born to a mother with lesions still present or treated less conservatively (ex. Not go to the NICU).

Old text (lines 86-92): "…it is reasonable to assume that neonates born to women with genital lesions during the third trimester of pregnancy that have resolved before delivery would be treated similarly, if not, less conservatively."

New text (lines 86-92): "…it is reasonable to assume that neonates born to women with genital lesions during the third trimester of pregnancy that have resolved before delivery would be treated similarly, under the assumption that it is a resolved recurrent infection with minimal risk of transmission."

b. The last paragraph seems to want to focus on the use of serology to help sort out first episode non-primary HSV infections. Would this group of women be expected to actually have a history of genital HSV? If not, then the purpose of the analysis is not really to focus on women with a positive HSV history. This should be clarified throughout the manuscript. Similarly, the title of the manuscript does not refer to the third trimester and should be adjusted if women with first episode non-primary infections do not have a clinical history of HSV.

Thank you for pointing this out as clarity regarding the population of interest in this study is paramount. The population under consideration is women who have a clinical history of genital HSV as well as an outbreak of lesions in the third trimester of pregnancy. Such individuals could either have HSV1 or HSV2 lesions in actuality, though it is common to consider genital HSV only HSV2. This underscores the importance of this study as women who actually had HSV2 and now have HSV1 are at much higher risk of vertical transmission to their neonates as are the women with HSV1 who now have HSV2. We have adjusted the title to incorporate the third trimester outbreak. We have also tried to edit the text throughout the manuscript to better reflect this population.

Old title: "Herpes Simplex Virus Serotyping in Pregnant Women with a History of Genital Herpes: A Cost-Effectiveness Analysis"

New title: “Herpes Simplex Virus Serotyping in Pregnant Women with a History of Genital Herpes and an Outbreak in the Third Trimester of Pregnancy: A Cost-Effectiveness Analysis”

c. Line 101: Consider replacing the words "...is cost effective" with "...could be cost effective" since the cost effectiveness determination can vary based on the various assumptions of the model used.

This is a good point. Thank you for clarifying and we have made the suggested change.

Old text (line 99): “…we sought to determine whether serology screening of women with a history of genital HSV and an outbreak in the third trimester of pregnancy is cost effective compared with no serology screening.”

New text (line 99): “we sought to determine whether serology screening of women with a history of genital HSV and an outbreak in the third trimester of pregnancy could be cost effective compared with no serology screening.”

3) Materials and Methods:
a. Lines 116-125: It appears that the women described in this paragraph had no history of genital HSV, which is somewhat incongruous with the previously stated goal of analyzing the cost effectiveness of serology in women with an outbreak during pregnancy and a history of HSV.

We thank the reviewer for noting any potential confusion. Throughout the manuscript and in the title, we have edited language to clarify that this population of interest was women with a stated history of genital HSV who experienced genital herpetic lesions during the third trimester.

b. How was the cost of the serology testing assigned and does it account for potential increased laboratory personnel/infrastructure needed to perform the additional tests.

Thanking for pointing this out, it is a good point that there may be additional costs associated with running serology including laboratory personnel/infrastructure. The cost was found by reviewing multiple cost-effectiveness analyses that used hospital specific databases to evaluate their locations cost of serology and all reported costs in the range of $6-$15 for serology. Similarly, the USPSTF estimates a cost between $10-40 for serology. We therefore decided to run our sensitivity analysis of the cost and found that the cost of serology would have to reach well above $1,300 for serology testing to no longer be cost effective. We have added this figure to the supplemental material and have noted it in the results.

c. Was there a sensitivity analyses performed based on how quickly the turn-around would be for serology, especially for those with an outbreak around delivery?

Thank you for this comment. After consideration, we believe this is less of a sensitivity analysis than a limitation of the test. The reviewer’s question, we believe is insightful

regarding peri-delivery lesions in that it is possible the test doesn't return in time to guide neonatal management in the setting of a non-primary first episode infection. It is a limitation that we addressed in our discussion and have now elaborated on further in both the discussion and results. We hope that in such a scenario, where tests that could inform treatment decisions are still pending, the neonate would be empirically treated. This means that some babies born to mothers with recurrent outbreaks may be unnecessarily treated until the test results return. One way of addressing this possible variation to our model is by varying the cost of acyclovir treatment, which we have done in a sensitivity analysis and found that the additional cost of neonatal workup and treatment could exceed $2,000 and still be cost effective.

We also considered the fact that the scenario of overtreating neonates could occur in the setting of false negative serology. Specifically, if a serology test comes back as a false negative, the mother may be presumed to have a primary outbreak and the neonate would therefore be treated. We evaluated the false negative rate in a sensitivity analysis as well and found that it could be higher than 50% without impacted the cost-effectiveness. In other words, over treating neonates does not appear to impact the cost-effectiveness of serology screening. It does raise an interesting question for future research: could be it be cost effective to empirically treat all neonates born to a mother with a history of HSV or lesions during pregnancy?

d. Line 183: What other conditions were used as a substitute for the utility estimates.

Thank you for this question. We have clarified the exact conditions used to estimate these utilities.

Old text (lines 187-188): "These were utility estimates of other conditions, because there were no utilities in the literature directly associated with HSV."

New text (lines 187-188): "These were utility estimates of a 10 day hospital stay, mild cerebral palsy, and moderate cerebral palsy, because there were no utilities in the literature directly associated with HSV."

4) Results:
a. Provide the number of additional serology tests that would be performed with the strategy of testing.

Thank you for this comment. The number of additional serology tests performed would be equal to the number of our population of interest, which we have estimated as 63,582.

b. Tables: Headings should be more descriptive.

Thank you for this comment. We have made the headings and titles more descriptive. Please let us know if we misunderstood this question or it needs further altering.

c. Table 1: Define the column heading value in the legend

Thank you for this comment. We do not have legends for our tables, only our figures, but have clarified the headings and titles. Please let us know if you were wanting us to add legends to the tables as well.

d. Table 3: Include in the column headings (N)

Thank you for pointing this out. We have added (N) following the headings serology screening and no serology screening in table 3.

e. Figure 1: The resolution of this image is poor and the words could not be interpreted.

We apologize for this and have uploaded new versions. Please let us know if the resolution continues to be poor.

f. Figure 2: The legend does not completely describe how to interpret 2 sides of the figure.

Thank you for pointing this out. We have added the following sentence for clarification: "The point at which the serology screening intervention passes the no serology screening branch is the point where the model would no longer predict a cost-effective outcome."

g. Figure 3: Spell out WTP in the legend

Thank you for bringing this to our attention. We have spelled out "willingness to pay" in that sentence.

5) Comments:
a. Would it be possible to use an estimated number of actual patients, rather than using a theoretic cohort of 100,000?

Thank you for bringing this up. We have re-evaluated our estimated cohort to try and better represent the population under study. Using estimates in the literature of the seroprevalence of HSV in women (26-40%), of the percent of seropositive individuals that experience symptomatic disease (5-36%), and off the percent with a history that get lesions in the third trimester (25%), as well as the CDC estimate of number of pregnant women in the United States in 2019, we have estimated a cohort via the following calculation. Taking the averages of the numbers provided: .33 x .20 x .25 x 3,853,472 = 63,582. We have updated our results to reflect this change.

Reviewer #3:

INTRODUCTION

In line 96 on page 6, you use the phrase "higher risk of vertical transmission." Higher than what? I think you mean, "higher than women with recurrent infection."

Thank you for commenting on this, you are correct. We have edited it to include the comparison.

Old text (lines 93-95): Currently, women with first episode non-primary infections have a higher risk of vertical transmission; yet, they undergo management guidelines put forth for recurrent, lower risk, HSV infections.

New text (lines 93-95): Currently, women with first episode non-primary infections have a higher risk of vertical transmission than women with recurrent infection; yet, they undergo management guidelines put forth for recurrent, lower risk, HSV infections.

DISCUSSION

Are you able to provide some estimate of how commonly serologic testing is used today in the specific framework you describe? Are the majority of pediatric units compliant with your "immediate treatment" recommendations for infants born to mothers with "initial, non-primary infection?"

I think your argument makes great sense, and, in fact, you convinced me that this protocol should be adopted provided that the pediatricians consistently modify their treatment based on the results of the serology.

Thank you so much for these comments. Pediatric units and NICUs are generally aggressive in treating suspected HSV. Serologic testing is generally uncommon, but perhaps based on the research, it will increase. The impact of such testing would be great to study in a large prospective cohort study.

STATISTICAL EDITOR COMMENTS:

lines 140-141: The study referenced included ~ 58K pregnant women, not ~ 583K and the numbers with HSV shedding and subsequent infected neonates were much less.

Thank you very much for catching that. We have adjusted it to be the correct number (58,362). We used this number as the study's original population under study, but you are correct that each unique scenario had smaller sample sizes. We hope we have been transparent about this in the discussion and newly added (N) column of Table 1. Please let us know if you feel it needs to further be addressed.

As the Authors note (lines 142-145), the samples related to probability estimates were actually small and one example that did not result in transmission cannot be generalized to zero risk of transmission. Should develop in more detail the risk estimates and their ranges, which could be in supplemental material. But these probabilities (and ranges) seem at least as crucial as the

probability of successful empiric antiviral treatment. Also need to justify the use of beta distribution for the probability estimates, particularly since some were based on small samples and a more liberal range might be justified.

Thank you for pointing this out. We agree that the sample sizes in Brown et. al (2003) are unfortunately quite small. Due to the fact that no RCTs can be ethically undertaken to replicate this study and given the nature of the rarity of neonatal HSV, much neonatal HSV research is based on these probabilities. We considered wide ranges for those values for this reason and found that the model was not significantly impacted by that variation, affording us some confidence in its strength despite the small sample sizes. Additionally, the one circumstance in which a transmission rate of 0 was used based on only 1 neonate was in the setting of a first episode HSV1 infection. If the probability of transmission is in fact anything greater than 0, it would strengthen our model, given that first episode-non primary infections are the transmissions of interest and intervention.

Beta distributions are commonly used for such model inputs in theoretical decision analyses. They are used because they estimate a normal distribution but remain between 0 and 1, which is necessary for probability and utility inputs.

lines 206-207: Should show the tornado analysis (could be in supplemental material) to show all the variables affected sensitivity analyses.

We have added the tornado analysis as a supplemental figure.

EDITOR'S COMMENTS:

Thank you for submitting your work to the Green Journal.

1) You state that there are ~1,500 neonatal infections a year in the United States. Do almost ~1,200 of them really arise (as you have modeled) from the 100,000 women with a history of herpes and active lesions in the third trimester? This seems too high a proportion. Are there data on this?

Thank you for pointing this out. This comment has helped us to re-evaluate our estimate of the theoretical cohort used in this study. While we were using an educated estimate before, we have reviewed the literature and come up with a more accurate calculation (laid out in response to comment 5, reviewer 2). The cohort we are now using is 63,582, which would contribute approximately 895 neonatal HSV cases to the 1,500 cited in the introduction. Of note, the 1,500 neonatal infections represent one conservative estimate of the total number of neonatal cases each year, giving a broad idea of the impact of this disease in the United States.

Though there is not a good estimate of how many cases of neonatal HSV currently come from which types of infection, the landmark study by Brown et. al in 2003 gives some insight into this. Out of 202 women who had positive viral cultures at delivery, there were

10 cases of neonatal HSV. Four of those cases were neonates born to mothers with a primary outbreak, four were born to mothers with a non-primary first episode outbreak, and 2 were born to mothers with recurrent outbreaks. Overall, this means 60% of cases fell into our study population. If applied to the 1,500 estimate, that would mean approximately 900 could come from our study population, which is similar to what our new cohort suggests.

Thank you for bringing up this insightful point as it helped us reach a cohort number we feel more confident with. Please let us know if you still feel this needs extra attention.

2) Please from the Title on make clear that it is women with both a history and active lesions in the third trimester that you are studying;

Thank you for this comment. We have altered the title to include the third trimester active lesions and have added clarifying wording throughout the manuscript. If we did not fully address this concern, we would be happy to change specific sentences that remain confusing.

3) Please make sure your model's approach to cesarean comports with ACOG's updated approach

Thank you for bringing this to our attention. The updated version says that women with non-primary first episode lesions in the third trimester can be offered a cesarean if they would like. As this came out in May, 2020, we will not have statistics on the number of women in this position who choose to deliver via cesarean vs vaginal and therefore would not know what probabilities to use in our model for mode of delivery. To get an idea of how this may affect our model, we have run a one way sensitivity analysis varying the probability of cesarean in first episode non-primary cases and found that even if every woman with a first episode non-primary outbreak in the third trimester opted for cesarean delivery, serology screening would remain cost effective. This has been updated in the results section lines 255-261. Interestingly, in order for this practice recommendation to be put into practice, women in our population under study would have to undergo serology screening to determine that they have a non-primary first episode infection and be able to be offered a cesarean.

EDITORIAL OFFICE COMMENTS:

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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 data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-obstetrics-data-definitions and the gynecology data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-gynecology-data-definitions. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

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* If all or part of the paper was presented at the Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists or at any other organizational meeting, that presentation should be noted (include the exact dates and location of the meeting).

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16. Figure 1: This will likely be difficult to fit in print. Please consider moving to supplemental digital content.

Thank you pointing this out. We have worked to reformat it so that it is less wide, as we believe it is integral to understanding our study design. Please let us know if it still does not fit with the new adjustments and we would be happy for it to be a supplemental figure.

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