

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)*

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obgyn@greenjournal.org.

Date: Nov 19, 2021
To: "Roxanne Hastie" [REDACTED]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-21-2106

RE: Manuscript Number ONG-21-2106

Aspirin for the prevention of birthing a small for gestational age infant; A Swedish register-based cohort study.

Dear Dr. Hastie:

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

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

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

Your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Dec 10, 2021, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1:

Summary: Register based cohort study to evaluate the potential of aspirin to decrease the risk of SGA infant or severe SGA infant in subsequent pregnancy. Large cohort of 8416 patients with 9.5% using aspirin in a subsequent pregnancy which revealed no effect on outcomes of SGA or severe SGA infant even after controlling for confounders. The study adds support to current ACOG and RCOG guidelines to not use previous SGA infant as a sole indication for LDA use. The large study adds to the literature about the potential utility of low dose aspirin for prevention of other diseases associated with placental pathologies.

1. Can line 124 be clarified? It did not make sense to me. "Preeclampsia in the first pregnancy was not included as a covariate within the subgroup analysis of preeclampsia in the first pregnancy."
2. Can the p-values be added for the comparative groups for table 1?
3. Recommend changing aspirin to indicate low dose aspirin throughout the manuscript although the exact dose is not known.
4. Additional limitations to acknowledge:
 - Lack of generalizability to other populations.
 - The lack of knowledge, inherent to a retrospective cohort study, of the indication for LDA with the subsequent pregnancy.

Reviewer #2: Aspirin for the prevention of birthing a small for gestational age infant: A Swedish register-based cohort study

Abstract: Authors clearly describe objectives of the study and conclude that ASA use does not improve risk for SGA in the setting of previous SGA baby.

Introduction: The authors do a good job explaining their rationale for their project
52 recommend changing to "severe SGA"

Methods:

65: Correlate Swedish national reference curve to measurement curve used in the United States.

72-79: Interesting that ethnicity was not described. The homogeneity of the population may not make this applicable to US practices

81-89: Was there any evaluation of looking at the variable "history of pregnancy complications (ie, GHTN, pre-E, GDM)" in 1st pregnancy affected by SGA?

92: dose of ASA different in Sweden than in US

109: Recommend moving discussion of power analysis from discussion to methodology and expand on how you got this number

Recommend expanding on current Swedish ASA guidelines these patients typically follow. Ie, 75mg daily starting at what gestation? What about if pre-E in current pregnancy? It would be helpful for US physicians to understand this.

Results:

Again, population is very homogenous but results are overall well described.

Discussion:

221-226: While discussion on potential for increased risk of bleeding should be mentioned, ACOG clinical guidelines reviewing ASA use in pregnancy show lower incidences of bleeding. Neonatal bleeding in both papers is extremely low (both <1%) and should be interpreted with caution.

Overall: very interesting data but based on a very particular population. Application to US populations, which show increased co-morbidities such as obesity, HTN/pre-E, etc may not be correlatable.

Reviewer #3: This is a cohort study comparing people with previous SGA neonate exposed and unexposed to aspirin in subsequent pregnancy. The primary outcome is recurrence of SGA in second pregnancy. Propensity scores are used to adjust for confounders. The authors found no association between aspirin use and risk of recurrent SGA. However, there are some findings in the data that call into question either the general practice patterns of aspirin use or the ascertainment of aspirin use that need further discussion.

1. Methods, all lines 92 to 99: is the validity of documentation of aspirin use on the prenatal chart previously confirmed? If not is it possible to do validation I have some percentage of charts to make sure that your exposure is correctly ascertained?

2. Methods, lines 102 to 106: the way you describe this it sounds a bit like you are re-calculating the 10th percentile for the specific group of individuals. Is this true, or are you simply stating what the standard deviation was for the population-based norm? Given that this has significant implications for the outcome of interest, please clarify.

3. Methods, statistical analysis: a confounder should be something both associated with the exposure and the outcome. Is country of birth associated with receipt of aspirin in Sweden? If not, it is not necessarily a confounder. Moreover, preeclampsia history certainly is a confounder, and I would strongly consider including it as a covariate.

4. Discussion, lines 221-226: I believe you are overstating the morbidity associated with aspirin. The Cochrane review has an RR of 1.06 (95% CI 1.00-1.12) for increased risk of EBL>500ml) and specifically states that this is "only slightly more." Consider attenuating your language choices here given overall minimal clinical implications.

5. Table 1: This table calls into question either the ascertainment of aspirin use or the general practice of aspirin use in Sweden. You have more than 50% of those with chronic hypertension, 85% of those with pregestational diabetes, 69% of those with chronic kidney disease, thrombosis or cardiovascular disease, and 42% of those with SLE NOT using aspirin. Moreover, 52% of those with previous preeclampsia are reported as not using aspirin. Is this true? I will admit not being deeply familiar with practice patterns in Sweden, but you do state that the recommendations support aspirin use in those with risk factors for preeclampsia. Either, these results tell me that people are not following practice recommendations or that your mode of ascertainment of exposure is flawed. Alternatively, recommendations for aspirin use may have come midway through your time period. If this is the case, please consider a time stratified analysis.

STATISTICAL EDITOR COMMENTS:

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

The study conclusions are valid re: the description of rates of SGA among the various groups (along with reporting relevant CIs), but it is underpowered to generalize the conclusions of no difference of SGA rates for the main group and its subsets. For example, using the counts in Table 2 for SGA (< 10th %-tile), stipulating an $\alpha = 0.05$ and power = 0.80, the minimum discernible difference from the baseline rate of 20.7% SGA would have to exceed 25.1% or be less than 16.5%. Put another way, there is ~ 25% stats power to discern a difference in relative rates of 10% and 74% power to discern a difference of 20% in relative rates of SGA. For the subset defined as SGA < 3rd % tile or the subsets listed in Table 3, the math is even less favorable, since the groups are even smaller. Also, for several of the subsets in Table 3, the aRR is likely overfitted, based on the number of adjustors vs the counts of SGA births.

EDITOR COMMENTS:

1. The Statistical Editor's comments must be fully addressed in your revision.
2. The Editors of Obstetrics & Gynecology have increased transparency around its peer-review process, in line with efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online. Additionally, unless you choose to opt out, we will also be including your point-by-point response to the revision letter. If you opt out of including your response, only the revision letter will be posted. Please reply to this letter with one of two responses:
 - A. OPT-IN: Yes, please publish my point-by-point response letter.
 - B. OPT-OUT: No, please do not publish my point-by-point response letter.
3. When you submit your revised manuscript, please make the following edits to ensure your submission contains the required information that was previously omitted for the initial double-blind peer review:
 - * Include your title page information in the main manuscript file. The title page should appear as the first page of the document. Add any previously omitted Acknowledgements (ie, meeting presentations, preprint DOIs, assistance from non-byline authors).
 - * Funding information (ie, grant numbers or industry support statements) should be disclosed on the title page and in the body text. For industry-sponsored studies, the Role of the Funding Source section should be included in the body text of the manuscript.
 - * Include clinical trial registration numbers, PROSPERO registration numbers, or URLs at the end of the abstract (if applicable).
 - * Name the IRB or Ethics Committee institution in the Methods section (if applicable).
 - * Add any information about the specific location of the study (ie, city, state, or country), if necessary for context.
4. Obstetrics & Gynecology uses an "electronic Copyright Transfer Agreement" (eCTA), which must be completed by all authors. When you uploaded your manuscript, each co-author received an email with the subject, "Please verify your authorship for a submission to Obstetrics & Gynecology." Please check with your coauthors to confirm that they received and completed this form, and that the disclosures listed in their eCTA are included on the manuscript's title page.
5. 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 Methods section of the body text, 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 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.
6. 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 randomized controlled trials (ie, CONSORT), observational studies (ie, STROBE), observational studies using ICD-10 data (ie, RECORD), meta-analyses and systematic reviews of randomized controlled trials (ie, PRISMA), harms in systematic reviews (ie, PRISMA for harms), studies of diagnostic accuracy (ie, STARD), meta-analyses and systematic reviews of observational studies (ie, MOOSE), economic evaluations of health interventions (ie, CHEERS), quality improvement in health care studies (ie, SQUIRE 2.0), and studies reporting

results of Internet e-surveys (CHERRIES). 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.

7. Your study uses ICD-10 data, please make sure you do the following:

- a. State which ICD-10-CM/PCS codes or algorithms were used as Supplemental Digital Content.
- b. Use both the diagnosis and procedure codes.
- c. Verify the selected codes apply for all years of the study.
- d. Conduct sensitivity analyses using definitions based on alternative codes.
- e. For studies incorporating both ICD-9 and ICD-10-CM/PCS codes, the Discussion section should acknowledge there may be disruptions in observed rates related to the coding transition and that coding errors could contribute to limitations of the study. The limitations section should include the implications of using data not created or collected to answer a specific research question, including possible unmeasured confounding, misclassification bias, missing data, and changing participant eligibility over time.
- f. The journal does not require that the title include the name of the database, geographic region or dates, or use of database linkage, but this data should be included in the abstract.
- g. Include RECORD items 6.3 and 7.1, which relate to transparency about which codes, validation method, and linkage were used to identify participants and variables collected.

8. 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.

9. 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 5,500 words. Stated word limits include the title page, précis, abstract, text, tables, boxes, and figure legends, but exclude references.

10. Titles in Obstetrics & Gynecology are limited to 100 characters (including spaces). Do not structure the title as a declarative statement or a question. Introductory phrases such as "A study of..." or "Comprehensive investigations into..." or "A discussion of..." should be avoided in titles. Abbreviations, jargon, trade names, formulas, and obsolete terminology also should not be used in the title. Titles should include "A Randomized Controlled Trial," "A Meta-Analysis," or "A Systematic Review," as appropriate, in a subtitle. Otherwise, do not specify the type of manuscript in the title.

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

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

12. Provide a short title of no more than 45 characters, including spaces, for use as a running foot.

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

14. 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.

15. 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.

16. 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%).

17. 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.

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

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

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

19. 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.

20. 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>.

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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 as a Microsoft Word document. Your revision's cover letter should include the following:

- * A confirmation that you have read the Instructions for Authors (<http://edmgr.ovid.com/ong/accounts/authors.pdf>), and

- * A point-by-point response to each of the received comments in this letter. Do not omit your responses to the Editorial Office or Editors' comments.

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

Again, your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Dec 10, 2021, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Jason D. Wright, MD
Editor-in-Chief, Elect

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

In compliance with data protection regulations, you may request that we remove your personal registration details at any time. (Use the following URL: <https://www.editorialmanager.com/ong/login.asp?a=r>). Please contact the publication office if you have any questions.

Dear Dr Wright,

Re: Manuscript Number ONG-21-2106: Aspirin for the prevention of birthing a small for gestational age infant; A Swedish register-based cohort study.

We thank the reviewers for their comments and for the opportunity to respond.

We look forward to your further correspondence in due course.

Kind regards,

Dr Roxanne Hastie, corresponding author

Reviewer #1:

Summary: Register based cohort study to evaluate the potential of aspirin to decrease the risk of SGA infant or severe SGA infant in subsequent pregnancy. Large cohort of 8416 patients with 9.5% using aspirin in a subsequent pregnancy which revealed no effect on outcomes of SGA or severe SGA infant even after controlling for confounders. The study adds support to current ACOG and RCOG guidelines to not use previous SGA infant as a sole indication for LDA use. The large study adds to the literature about the potential utility of low dose aspirin for prevention of other diseases associated with placental pathologies.

We thank the reviewer for these comments.

1. Can line 124 be clarified? It did not make sense to me. "Preeclampsia in the first pregnancy was not included as a covariate within the subgroup analysis of preeclampsia in the first pregnancy."

We have now clarified Line 157 to read:

"Within the subgroup analyses stratified by whether women developed preeclampsia in their first pregnancy or not, preeclampsia status of the first pregnancy was not included as a covariate."

2. Can the p-values be added for the comparative groups for table 1?

P-values have been added to Table 1.

3. Recommend changing aspirin to indicate low dose aspirin throughout the manuscript although the exact dose is not known.

Amended throughout.

4. Additional limitations to acknowledge:

--Lack of generalizability to other populations.

--The lack of knowledge, inherent to a retrospective cohort study, of the indication for LDA with the subsequent pregnancy.

Additional limitations have been included from line 282, which reads:

"Additionally, these findings may not be generalizable to other non-Swedish populations. Lastly, information of the dosage of aspirin used, indication and adherence were not captured within our dataset and there is potential for maternal under reporting and ascertainment bias."

Reviewer #2:

Abstract: Authors clearly describe objectives of the study and conclude that ASA use does not improve risk for SGA in the setting of previous SGA baby.

We thank the reviewer for their review and these comments.

Introduction: The authors do a good job explaining their rationale for their project line 52 recommend changing to "severe SGA"

Thank you for highlighting this error, line 52 has been amended.

Methods:

65: Correlate Swedish national reference curve to measurement curve used in the United States.

Both Sweden and the United States use population based curves standardized for sex and gestational age at birth, with infants born <10th percentile considered SGA. Although the curves differ due to different reference population, they have similar methodology and z-score cut offs for defining the 10th percentile (1.282 vs 1.311).

We have referred to the US curves within the methods line 135:

"The primary outcome was SGA birth, defined as infant birthweight <10th percentile which was based upon the Swedish population normal distribution and sex-specific standardized birthweight percentiles(10), which is similar to the commonly used US population based curve(11)."

72-79: Interesting that ethnicity was not described. The homogeneity of the population may not make this applicable to US practices

Further details of country of birth have been included in Table 1 and generalizability of these findings included as a potential limitation on Line 282 of the discussion:

"Additionally, these findings may not be generalizable to other non-Swedish populations."

81-89: Was there any evaluation of looking at the variable history of pregnancy complications (ie, GHTN, pre-E, GDM) in 1st pregnancy affected by SGA?

Previous pregnancy complications were included as covariates within our adjusted models but not analyzed separately for their association with a subsequent SGA birth.

92: dose of ASA different in Sweden than in US

Yes, this is correct. In Sweden, low dose aspirin use during pregnancy is recommended at 75 mg, which is lower than US recommendations.

This difference is acknowledged within the discussion from Line 285:

"However, in Sweden aspirin is routinely prescribed at 75mg during pregnancy. Further investigations using other populations and of higher doses, including 150mg, are still required and large randomized clinical trials investigating aspirin for the primary prevention of SGA are warranted."

109: Recommend moving discussion of power analysis from discussion to methodology and expand on how you got this number

We have now included further detail of the a-priori power calculation within the methods on Line 140 which reads:

"An a-priori power calculation was included with our statistical analysis plan that showed given a sample size of 8,416, 801 in the exposed group and stipulating an alpha of 0.05 and power of 0.80, the minimum detectable absolute risk difference between the groups was 4.35%."

Recommend expanding on current Swedish ASA guidelines these patients typically follow. I.e, 75mg daily starting at what gestation? What about if pre-E in current pregnancy? It would be helpful for US physicians to understand this.

We have now included further details of current Swedish guidelines for aspirin use during pregnancy. Line 119 now reads:

"National Swedish guideline recommend 75 mg of aspirin daily for the women at high risk of preeclampsia or with several moderate risk factors, based on NICE guidelines, from 12 weeks through until 36 weeks' gestation. Women with other indications for aspirin use such as systemic lupus erythematosus or other chronic disease may also be treated with aspirin. In Sweden, aspirin is not started after the onset of preeclampsia and in most centers, treatment is stopped when preeclampsia is diagnosed. There are no national guidelines surrounding aspirin for the prevention of SGA or preterm birth, and use for these indications is determined by the treating clinician."

Discussion:

221-226: While discussion on potential for increased risk of bleeding should be mentioned, ACOG clinical guidelines reviewing ASA use in pregnancy show lower incidences of bleeding. Neonatal bleeding in both papers is extremely low (both <1%) and should be interpreted with caution.

We agree with the reviewer that the incidence of neonatal bleeding in these papers was too low to draw meaningful conclusions and have thus not included discussion of this. Additionally, given the uncertainty regarding the level of bleeding risk associated with aspirin use we have not quantified this and rather stated women *may* be at increased risk.

Overall: very interesting data but based on a very particular population. Application to US populations, which show increased co-morbidities such as obesity, HTN/pre-E, etc may not be correlatable.

We agree with the reviewer that these findings may not be applicable to other populations and have acknowledged this as a potential limitation from Lines 282 and 285:

"Additionally, these findings may not be generalizable to other non-Swedish populations"

"Further investigations using other populations and of higher doses, including 150mg, are still required"

Reviewer #3:

This is a cohort study comparing people with previous SGA neonate exposed and unexposed to aspirin in subsequent pregnancy. The primary outcome is recurrence of SGA in second pregnancy. Propensity scores are used to adjust for confounders. The authors found no association between aspirin use and risk of recurrent SGA. However, there are some findings in the data that call into question either the general practice patterns of aspirin use or the ascertainment of aspirin use that need further discussion.

1. Methods, all lines 92 to 99: is the validity of documentation of aspirin use on the prenatal chart previously confirmed? If not is it possible to do validation I have some percentage of charts to make sure that your exposure is correctly ascertained?

Yes, the validity of medication use recorded within the Swedish Pregnancy Register, which was used to obtain the data for this study, has been previously validated against the National Pharmacy Database (records data of all dispensed medications in Sweden) and found to have a high level of

agreement between antenatal records and the National Pharmacy Database (up to 86%). See DOI: [10.2147/CLEP.S16305](https://doi.org/10.2147/CLEP.S16305)

As with all retrospective cohort studies there is the potential for ascertainment bias, which is acknowledged as a limitation from Line 283:

“Lastly, information of the dosage of aspirin used and adherence were not captured within our dataset and there is potential for maternal under reporting and ascertainment bias.”

2. Methods, lines 102 to 106: the way you describe this it sounds a bit like you are re-calculating the 10th percentile for the specific group of individuals. Is this true, or are you simply stating what the standard deviation was for the population-based norm? Given that this has significant implications for the outcome of interest, please clarify.

We did not re-calculate the 10th percentile for this sample, and this rather refers to the population based normal distribution.

We have now clarified this from Line 135 to read:

“The primary outcome was SGA birth, defined as infant birthweight <10th percentile which was based upon the Swedish population normal distribution and sex-specific standardized birthweight percentiles(10). The secondary outcome was severe SGA birth, defined as the <3rd percentile.”

3. Methods, statistical analysis: a confounder should be something both associated with the exposure and the outcome. Is country of birth associated with receipt of aspirin in Sweden? If not, it is not necessarily a confounder. Moreover, preeclampsia history certainly is a confounder, and I would strongly consider including it as a covariate.

The reviewer is correct; country of birth is not directly associated with aspirin use. However, given the association between country of birth and maternal BMI, age and pre-gestational disorders we have included this within our model as per our a-priori statistical analysis plan and direct acyclic graph. Additionally, outcomes of the first pregnancy, including preeclampsia, were included in adjusted model as stated on line 153:

“Included covariates were: maternal age, body mass index, smoking status, country of birth, in-vitro fertilization, pre-gestational disorders (pre-existing hypertension, cardiovascular disease, systemic lupus erythematosus, thrombosis), gestational diabetes and first pregnancy outcomes (preeclampsia, birth of an infant<3rd percentile (interacted with preeclampsia) stillbirth, preterm birth).”

4. Discussion, lines 221-226: I believe you are overstating the morbidity associated with aspirin. The Cochrane review has an RR of 1.06 (95% CI 1.00-1.12) for increased risk of EBL>500ml) and specifically states that this is "only slightly more." Consider attenuating your language choices here given overall minimal clinical implications.

In addition to the 2019 Cochrane review, we have previously reported that aspirin use during pregnancy, among a Swedish population, was associated with a 2-fold increased odds of post-partum hemorrhage and recently updated ISSHP guidelines also recognize this potential risk. Together these findings suggest that there may be an increased risk. However, we have now reduced the emphasis of this by stating women may be at increased risk. Line 255 now reads:

“Previously, we have reported aspirin to be associated with an increased risk of maternal bleeding, including postpartum hemorrhage and postpartum hematoma(14). Additionally, a slight increased risk of postpartum hemorrhage was reported in the 2019 Cochrane systematic review of antiplatelet agents for the prevention of preeclampsia(2). Thus, the use of aspirin for preventing SGA may have little benefit and may place women at an increased risk of intra- and postpartum bleeding complications.”

5. Table 1: This table calls into question either the ascertainment of aspirin use or the general practice of aspirin use in Sweden. You have more than 50% of those with chronic hypertension, 85% of those with pregestational diabetes, 69% of those with chronic kidney disease, thrombosis or cardiovascular disease, and 42% of those with SLE NOT using aspirin. Moreover, 52% of those with previous preeclampsia are reported as not using aspirin. Is this true? I will admit not being deeply familiar with practice patterns in Sweden, but you do state that the recommendations support aspirin use in those with risk factors for preeclampsia. Either, these results tell me that people are not following practice recommendations or that your mode of ascertainment of exposure is flawed. Alternatively, recommendations for aspirin use may have come midway through your time period. If this is the case, please consider a time stratified analysis.

Yes, although the true ascertainment of aspirin use cannot be determined given the retrospective nature of this study, these figures are likely correct and reflect prescribing practices of aspirin in Sweden during the study period. During the study period, the evidence-based guidelines for preeclampsia from the Swedish Society of Obstetrics and Gynecology were not yet in place, however there was a recommendation from a working group within the Society about aspirin prophylaxis in pregnancy. In Sweden, the screening of high risk women occurs in the maternal health care centers by midwives and during the study period, centers did not have an equal screening policy and in general there was a higher threshold for aspirin use. During the study period, across the entire pregnant population, aspirin use was found at 1 – 2%, which has increased to 10% under the new Swedish guidelines.

For the chronic diseases, women with prior thrombotic events and chronic kidney disease (such as repeated infections) are not offered aspirin as per Swedish guidelines. In addition, since this study relies on retrospective data, there is the potential for under reporting and ascertainment bias of aspirin use, which we have acknowledged on line 283 of the discussion:

“Lastly, information of the dosage of aspirin used and adherence were not captured within our dataset and there is potential for maternal under reporting and ascertainment bias.”

Statistical editor comments:

The study conclusions are valid re: the description of rates of SGA among the various groups (along with reporting relevant CIs), but it is underpowered to generalize the conclusions of no difference of SGA rates for the main group and its subsets. For example, using the counts in Table 2 for SGA (< 10th %-tile), stipulating an $\alpha = 0.05$ and power = 0.80, the minimum discernible difference from the baseline rate of 20.7% SGA would have to exceed 25.1% or be less than 16.5%. Put another way, there is ~ 25% stats power to discern a difference in relative rates of 10% and 74% power to discern a difference of 20% in relative rates of SGA. For the subset defined as SGA < 3rd % tile or the subsets listed in Table 3, the math is even less favorable, since the groups are even smaller. Also, for several of the subsets in Table 3, the aRR is likely overfitted, based on the number of adjustors vs the counts of SGA births.

We thank the statistical editor for their review and agree with their calculations. We had performed an a-priori power calculation within our statistical analysis plan and have now included this within the methods, Line 140:

“An a-priori power calculation was included with our statistical analysis plan that showed given a sample size of 8,416, 801 in the exposed group and stipulating an alpha of 0.05 and power of 0.80, the minimum detectable absolute risk difference would be 4.35%.”

We have acknowledged the power of our study as a limitation, recognized that subgroup analyses should be considered explorative or tentative findings and altered our conclusion to better reflect our findings of no detectable difference rather than no difference.

Line 281 now reads:

“Our study was sufficiently powered to detect an absolute difference of 4.35%. Thus, it is plausible that aspirin may have had a smaller protective effect that was not detected in this population. Additionally, power within subgroup analyses was substantially reduced and these findings should be considered explorative and may add to future meta-analyses.”

Line 291 reads:

“In this population register-based cohort study, the use of aspirin among women who previously birthed an SGA infant, was not associated with a detectable difference in the risk of subsequent SGA birth. Our data does not support previous SGA alone as an indication for subsequent aspirin use.”

Regarding overfitting, we agree with the reviewer that overfitting will occur if the model is too highly tuned to the data or that among a small number of cases any special features may lead to highly influential propensity scores and consequently large inverse probability weighting. We agree this is a concern, however less so within our analyses as we have shown the propensity score model fits the data well in the overall analysis and subgroup analyses. This is demonstrated by the achieved covariate balance of each model (online supplement) and sufficient overlap of score. We have also stated that subgroup analyses should be considered explorative/tentative results.

Editor comments:

1. The Statistical Editor's comments must be fully addressed in your revision.

Addressed as per above.

2. The Editors of Obstetrics & Gynecology have increased transparency around its peer-review process, in line with efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online. Additionally, unless you choose to opt out, we will also be including your point-by-point response to the revision letter. If you opt out of including your response, only the revision letter will be posted.

A OPT-IN: Yes, please publish my point-by-point response letter.

7. Your study uses ICD-10 data, please make sure you do the following:
a. State which ICD-10-CM/PCS codes or algorithms were used as Supplemental Digital Content.
b. Use both the diagnosis and procedure codes.
c. Verify the selected codes apply for all years of the study.

List of ICD-10 codes are now included in the online supplemental file.
Selected codes apply for all years of the study.

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

Included on line 55:

Précis: Among women with a history of birthing an SGA infant, low dose aspirin was not associated with an altered risk of a subsequent SGA birth.

In addition, the abstract length should follow journal guidelines. The word limit for Original Research articles is 300 words. Please provide a word count.

Abstract word count: 300