OBSTETRICS & GYNECOLOGY

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

Date: Jun 14, 2019
To: "Alexander M Friedman" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-19-852

RE: Manuscript Number ONG-19-852

Antibiotic use without indication during delivery hospitalizations in the United States

Dear Dr. Friedman:

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

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

Your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Jul 05, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: The authors present an analysis of a large commercial inpatient database to examine trends in antibiotic administration at the time of delivery. They focus on the use of antibiotics during hospitalizations for delivery, although the primary outcome of interest is somewhat unclear. They discuss overall trends during what seems to be a convenience timeframe based on the availability of the data set rather than one driven by specific major practice changes.

Specific Considerations:

1. Throughout the manuscript the authors refer to "antibiotic use during vaginal delivery hospitalization without an evidence-based indication for antibiotic administration". This would be more reader friendly if consolidated to "use of antibiotics without indication" or a similar less wordy phrasing.

2. Methods-- is it possible to describe in more detail the data validation process for the database? If not validated at the chart review level, then what was done?

3. The reason for exclusion of third and fourth degree lacerations and retained placenta is unclear. These are indications for administration of antibiotics , so if the diagnosis is present and antibiotics were given those antibiotics are not without an evidence-based indication for antibiotic administration.

4. The discussion of erythromycin is unclear. Erythromycin may be given in the setting of PPROM so the statement on lines 223-224 needs some further clarification if those diagnoses are not included in the analysis or do not correlate with erythromycin administration. Similarly on 231-233 a reference is needed to substantiate the statement that penicillin allergy is "the most likely indication for maternal indication (sic) of erythromycin."

5. Sentence on lines 357-362 is very long and difficult to follow, unclear.

6. In the discussion the authors should consider the possibility that the change observed may represent an improvement in data quality rather than a change in practice over time.

7. In table 1, the denominator for the (%) is unclear. Is this the percent of the total population, or of the subset in the column, or other? Consider breaking out the demographics table, to be followed by a table showing the categories of antibiotic administration for simplicity.

Reviewer #2: The authors aim to evaluate trends in antibiotic use after vaginal delivery without an indication for

antibiotics. The manuscript needs a careful proofread for typos. I have the following additional comments regarding the manuscript:

Abstract

1. I know word count is often the limitation with abstracts. But it would be nice if the authors could include one background sentence to help the reader understand the context for this research question. What prompted you to look at this? Why does it matter?

Intro

2. Line 126. Consider instead "infection morbidity" rather than "infectious morbidity" as morbidity itself is not infectious.

3. Line 144. Can the authors reference the evidence-based recommendations that they are referring to? This may help with understanding the observed trend over years. For example, change in practice may occur after specific guidelines are released.

Methods

4. Line 160. Change "data was" to "data were" since the word data is plural.

5. Line 174. Can the ICD9 codes that were utilized for identification of diagnoses requiring antibiotics be provided? Perhaps as a supplemental table.

6. It is going to be really hard to get at whether antibiotics were "evidence-based" or not using diagnostic code data. For example, if women are GBS unknown and in preterm labor they would receive GBS prophylaxis. But would not have a code of GBS colonization.

7. Line 188. Some of the included antibiotics are contraindicated during pregnancy (eg fluoroquinolones, tetracyclines). What was the rationale for including them? If anything, I would exclude women who received these as I would be concerned about inaccurate data.

8. Line 201. What about looking at preterm delivery or gestational age at delivery rather than just preterm labor?

Results

9. Line 242-244. The prevalence of all the indications seems low which makes me worry about using this methodology to delineate "evidence-based" antibiotics versus not. Would expect GBS colonization to be 20-30%, PPROM to be more like 3%, chorio 5-10% and so on. I suspect there is a misclassification of women into receiving antibiotics that were not evidence-based because infection complications are under-coded.

10. Line 256. It seems problematic that women who had an indication for antibiotics were less likely to receive them over the study time period. Is this artifact? Or representative of changes in the way antibiotics were captured in the database over time that may also affect the other groups studied?

11. Line 262. Do you think that amp/PCN were women who were GBS unknown but did meet criteria for prophylaxis or the rest of the GBS positive group that was just not coded appropriately?

Reviewer #3: This is a well-conceived and executed analysis of a large administrative data set.

Comments and questions:

1. Was there any information to examine who performed the delivery? An OB GYN, a non-OB GYN physician, or a non-physician?

2. A limitation of the study is the inability to ascertain whether the antibiotics were administered antepartum, intrapartum or postpartum.

3. I may have missed the definition of prolonged ruptured membranes as an evidence-based indication related to the intrapartum risk of GBS. Was this common outcome included in the analysis?

STATISTICAL EDITOR'S COMMENTS:

1. Tables 1 and 2: This is a large study, and subsets are also generally very large. However, the subsets for race designation "Unknown" have relatively small counts and the aRR may be overfitted. Suggest omitting that analysis (the aRR) from Table 2. Also, given the large number of comparisons in Table 2, should uniformly apply a stricter inference threshold and cite stricter CIs than 95% CI, due to mulitple hypothesis testing and concern re: spurious associations. I believe most associations will still stand the inference testing.

2. Figs 1, 2: Since the data are given for each year as a unit, rather than continuously, it would be better to show the changing proportions as a series of dots or some other symbol at the year intervals.

3. General: There were > 3 million deliveries analyzed from over an almost 10 year period. Likely some of those deliveries were repeats for individual women. It is possible that the previous practice of receiving/not receiving antibiotics in an individual may tend to correlate with the next pregnancy. Should either (1) randomly chose one pregnancy per woman to preserve independence (2) or adjust for any correlation of those events (3) or as a sensitivity analysis, just evaluate women with one pregnancy and compare results with the entire cohort described.

EDITORIAL OFFICE COMMENTS

1. The Editors of Obstetrics & Gynecology are seeking to increase transparency around its peer-review process, in line with efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online. Additionally, unless you choose to opt out, we will also be including your point-by-point response to the revision letter. If you opt out of including your response, only the revision letter will be posted. Please reply to this letter with one of two responses:
A. OPT-IN: Yes, please publish my point-by-point response letter.
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2. As of December 17, 2018, Obstetrics & Gynecology has implemented an "electronic Copyright Transfer Agreement" (eCTA) and will no longer be collecting author agreement forms. When you are ready to revise your manuscript, you will be prompted in Editorial Manager (EM) to click on "Revise Submission." Doing so will launch the resubmission process, and you will be walked through the various questions that comprise the eCTA. Each of your coauthors will receive an email from the system requesting that they review and electronically sign the eCTA.

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

3. Our journal requires that all evidence-based research submissions be accompanied by a transparency declaration statement from the manuscript's lead author. The statement is as follows: "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." *The manuscript's guarantor.

If you are the lead author, please include this statement in your cover letter. If the lead author is a different person, please ask him/her to submit the signed transparency declaration to you. This document may be uploaded with your submission in Editorial Manager.

4. In order for an administrative database study to be considered for publication in Obstetrics & Gynecology, the database used must be shown to be reliable and validated. In your response, please tell us who entered the data and how the accuracy of the database was validated. This same information should be included in the Materials and Methods section of the 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 randomized controlled trials (ie, CONSORT), observational studies (ie, STROBE), 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, 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 and gynecology data definitions at https://www.acog.org/About-ACOG/ACOG-Departments/Patient-Safety-and-Quality-

Improvement/reVITALize. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

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

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* 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. Provide a short title of no more than 45 characters (40 characters for case reports), including spaces, for use as a running foot.

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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 Jul 05, 2019, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

The Editors of Obstetrics & Gynecology

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

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