

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.*

Personal or nonessential information may be redacted at the editor's discretion.

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

Date: Mar 18, 2020
To: "Jeffrey Benjamin Gould" [REDACTED]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-20-228

RE: Manuscript Number ONG-20-228

Time of Birth and the Risk of Severe Unexpected Complications in Term Singleton Newborns

Dear Dr. Gould:

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 Apr 08, 2020, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: This article supports long held suspicions of those in active practice of Obstetrics & Gynecology that there is a relationship between birth timing and the risk of adverse outcomes. The size of the population sample creates confidence that the results are representative. However it appears that previous cesarean section, and trial of labor after caesarean section are not included in this analysis. Given that uterine rupture is likely a meaningful contributor the rate of unexpected neonatal complications at term this data should be included. Therefore onset of labor (spontaneous, induction, or no-labor) and route of birth (vaginal delivery, operative vaginal delivery (vacuum or forceps), failed operative vaginal delivery with subsequent cesarean section, failed trial of labor with subsequent cesarean section, elective repeat cesarean section, and elective primary cesarean section), if possible, need be included and adjusted for in the analysis. Inclusion of this data may exacerbate or ameliorate any the effect size of birth timing, and certainly may represent regional practice differences. However if not possible from the data available, this limitation should be expressed more specifically than a generic comment regarding unknown maternal or fetal factors. In addition, specific commentary regarding variability in staffing paradigms, such as the move to Obstetrical 24hr in house Hospitalist programs with 24hr in house Anesthesia support, need be included as things that may relate to some of the regional factors seen in the analysis.

Reviewer #2: This study makes good use of the very large numbers of birth in California examine severe unexpected neonatal morbidity by day and time of day. The authors are clear to make the point that variations within such a large dataset may be an opportunity for quality improvement if some hospitals/areas demonstrate no differences in events by day and time of day. Such an analysis would not be possible with such large numbers. Methods are easy to follow and the analytic approach is appropriate for the analysis and the figures add to the understanding of the results and illustrate their potential usefulness as an approach to improving quality of care. This reviewer has no substantive revisions except found the abbreviation SUNC difficult to understand in the beginning. It is spelled out in the abstract but not in the paper when the first time it is used.

Reviewer #3: Gould and colleagues present findings from a retrospective birth certificate/hospital discharge data study designed to evaluate the relationship between off hour births and severe unexpected neonatal morbidity in low risk term singleton infants. The authors utilized administrative data derived from birth certificates and hospital discharge data from California from 2011-2013. The authors evaluated the relationship of time and day of birth and assessed differences between perinatal care regions in California. The primary outcome was defined according to an established metric for severe unexpected neonatal morbidity. The authors noted increased risk for severe unexpected neonatal morbidity among babies born 3pm-11 pm and 11 pm and 7 am. Increased risk was also noted for deliveries which occurred on Sunday. A point by point critique of the paper follows:

- 1) In the Abstract of the paper, the "night shift" is not defined. It would improve readability to provide the definition similar to the other categories noted on lines 35-36 of the paper.
- 2) The objective of the study was stated to evaluate the relationship of "off hour" births with severe unexpected neonatal morbidity. The authors evaluated 3 time intervals in their study: 7 am - 3 pm, 3 pm - 11 pm, 11 pm and 7 am. What interval was considered "Off hours" for their primary objective of the study. The authors also use the terms "day shift", "evening shift" and "night shift" in the paper. The terminology used in the paper should be consolidated and be consistent in the revised paper. The objective of the paper should also be clarified as well with respect to what "off hours" is considered for the purpose of the study.
- 3) For the 3 study time intervals, the transitional times include 2 time interval categories. For instance, a delivery at 7 am would have been included in the 7 am - 3 pm group and the 11 pm - 7 am group as defined in the paper. How did the authors handle the deliveries that occurred at the transitional times? This should be more clearly specified in the revised paper.
- 4) The authors noted difference existed between 2 perinatal care regions. Are there any known characteristics between these 2 perinatal care regions with respect to distribution of specific neonatal levels of care, acuity of patients, racial/ethnic disparities which are available and can be assessed in relation to the observation noted. It would be helpful to explore this issue since the observation was reported and hospital level data would be available on the level of the perinatal care region.

STATISTICAL EDITOR'S COMMENTS:

1. Abstract: Should include concise summary of absolute risks by shift, rather than just as aORs.
2. Table 1: Should include some stats comparisons of baseline characteristics for daytime vs other shifts.
3. Table 2: Should include in footnote a complete list of which variables were included in the final aOR models. Also, the analysis by day of week compared 6 days vs Monday as the referent, but without any adjustment for multiple hypothesis testing. Although plausible that the same issues might occur on Sunday rather than on other days of the week that occur on non-daytime shifts, this association is weaker than the main point and needs to be acknowledged. Should include a stricter threshold for inference testing for analysis by day of week.
4. Table 3: Again, no adjustment for testing multiple hypotheses (36 in this Table) increases probability of some spurious associations, while also diluting the sample sizes so that there is less power to detect infrequent events.
5. Fig 1 and Table 2: The odds ratios cited in Table 2 show an increase for evening and night shifts, while the right hand y-axis in Fig 1 A and B both show a decrease in odds. Need to clarify.

EDITORIAL OFFICE COMMENTS:

1. The Editors of Obstetrics & Gynecology are seeking to increase transparency around its peer-review process, in line with efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online. Additionally, unless you choose to opt out, we will also be including your point-by-point response to the revision letter. If you opt out of including your response, only the revision letter will be posted. Please reply to this letter with one of two responses:
 - A. OPT-IN: Yes, please publish my point-by-point response letter.
 - B. OPT-OUT: No, please do not publish my point-by-point response letter.
2. As of December 17, 2018, Obstetrics & Gynecology has implemented an "electronic Copyright Transfer Agreement" (eCTA) and will no longer be collecting author agreement forms. When you are ready to revise your manuscript, you will be prompted in Editorial Manager (EM) to click on "Revise Submission." Doing so will launch the resubmission process, and you will be walked through the various questions that comprise the eCTA. Each of your coauthors will receive an email from the system requesting that they review and electronically sign the eCTA.

Please check with your coauthors to confirm that the disclosures listed in their eCTA forms are correctly disclosed on the manuscript's title page.

3. Was this study presented at the International Perinatal Collegium? If so, please disclose the name, date/s, and location of the meeting on the title page of your manuscript.
4. 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.

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

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

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

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

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

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

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

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

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

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

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

13. The Journal's Production Editor had the following to say about this manuscript:

"Figure 1: Please upload as a high resolution figure file on Editorial Manager."

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.

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

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

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 21 days from the date of this letter. If we have not heard from you by Apr 08, 2020, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

The Editors of Obstetrics & Gynecology

2018 IMPACT FACTOR: 4.965

2018 IMPACT FACTOR RANKING: 7th out of 83 ob/gyn journals

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

RE: Revision for Manuscript Number ONG-20-228

Time of Birth and the Risk of Severe Unexpected Complications in Term Singleton Newborns

Dear Editors,

On behalf of the co –authors who approve the revision I am pleased to submit our revised manuscript.

We submit this revision solely to Obstetrics and Gynecology and attest that it is not under consideration at any other journals.

Furthermore, the lead author, Jeffrey Gould MD, affirms that this revised manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

The IRB of Stanford University School of Medicine approved this study.

Permission to submit this manuscript to Obstetrics and Gynecology has been obtained from all of the authors.

We thank the reviewers for their many helpful suggestions and have incorporated them into the revised manuscript. Following the recommendation of the statistical editor, we have recalculated our findings to account for multiple comparisons, as well as addressing the additional comments. In preparing the revision, we have read and followed the instructions for authors. Below is a point-by-point response to each of the received comments.

Thank you for considering our revision, Jeffrey B Gould MD, MPH 4/7/2020

REVIEWER COMMENTS:

Reviewer #1:

- A. However it appears that previous cesarean section, and trial of labor after caesarean section are not included in this analysis. Given that uterine rupture is likely a meaningful contributor the rate of unexpected neonatal complications at term this data should be included. Therefore

onset of labor (spontaneous, induction, or no-labor) and route of birth (vaginal delivery, operative vaginal delivery (vacuum or forceps), failed operative vaginal delivery with subsequent cesarean section, failed trial of labor with subsequent cesarean section, elective repeat cesarean section, and elective primary cesarean section), if possible, need be included and adjusted for in the analysis. Inclusion of this data may exacerbate or ameliorate any the effect size of birth timing, and certainly may represent regional practice differences. **However if not possible from the data available, this limitation should be expressed more specifically than a generic comment regarding unknown maternal or fetal factors.**

Response: We now explain that c section was not used as a risk adjuster because it occurred after admission on the decision of the provider on line 105. As advised by the reviewer, in our limitations section on line 196 we are now more specific concerning unknown risk factors.

- B.** In addition, specific commentary regarding variability in staffing paradigms, such as the move to Obstetrical 24hr in house Hospitalist programs with 24hr in house Anesthesia support, **need be included as things that may relate to some of the regional factors seen in the analysis.**

Response: On Line 189, we now state that an analysis of the potential regional differences that could contribute to the increase in sUNC in now 4 of the 9 regions in process and list some of the possible factors as described by the reviewer.

Reviewer #2:

- A.** This reviewer has no substantive revisions except found **the abbreviation sUNC** difficult to understand in the beginning. It is **spelled out in the abstract but not in the paper when the first time it is used.**

Response: When unexpected severe neonatal morbidity is first used on line 71 we have followed it with (sUNC) as requested.

Reviewer #3:

- 1) In the **Abstract of the paper, the "night shift" is not defined.** It would improve readability to **provide the definition** similar to the other categories noted on lines 35-36 of the paper.

Response: The temporal definition of night shift (11pm -7am) is now included on line 36.

- 2) The objective of the study was stated to evaluate the relationship of "off hour" births with severe unexpected neonatal morbidity. The authors evaluated 3 time intervals in their study: 7 am - 3 pm, 3 pm - 11 pm, 11 pm and 7 am. What interval was considered "Off hours" for their primary objective of the study. The authors also use the terms "day shift", "evening shift" and "night shift" in the paper. **A. The terminology used in the paper should be consolidated and be consistent in the revised paper. B. The objective of the paper should also be clarified as well with respect to what "off hours" is considered for the purpose of the study.**

Response: As suggested we have replaced off hours with the consistent use “evening, night, and weekend “ on the abstract at line 28, and in the text at lines 147 , 157, 163, 209, and 216.

3) For the 3 study time intervals, the transitional times include 2 time interval categories. For instance, a delivery at 7 am would have been included in the 7 am - 3 pm group and the 11 pm - 7 am group as defined in the paper. **How did the authors handle the deliveries that occurred at the transitional times? This should be more clearly specified in the revised paper.**

Response: the confusion was due to our notating the periods as, 7am-3pm, 3pm-11pm, and 11pm to 7am. We now explain on lines 105-107 that the time frames were 7am until 3pm , 3pm until 11pm , and 11pm until 7am and for ease of presentation these time frames are presented as 7am-3pm , 3pm-11pm, and 11pm-7am.

4) **The authors noted difference existed between 2 perinatal care regions. Are there any known characteristics between these 2 perinatal care regions with respect to distribution of specific neonatal levels of care, acuity of patients, racial/ethnic disparities which are available and can be assessed in relation to the observation noted.** It would be helpful to explore this issue since the observation was reported and hospital level data would be available on the level of the perinatal care region.

Response: On Line 189, we now state that an analysis of the potential regional differences that could contribute to the increase in sUNC in 4 of the 9 regions is in process and list some of the possible factors being considered.

STATISTICAL EDITOR'S COMMENTS:

1. Abstract: Should include concise summary of absolute risks by shift, rather than just as aORs.

Response: We modified the abstract as the following on Line 35:

“Severe unexpected neonatal morbidity was higher among births during the 3 pm-11 pm evening (2.1%) and the 11 pm-7 am night shift (2.1%) as compared to those during the 7 am-3 pm day shift (1.8%). The adjusted odds ratio (AOR) were 1.10 (95% confidence interval [CI95] = 1.06-1.13) for the evening shift and 1.15 (1.11-1.19) for the night shift.”

2. Table 1: Should include some stats comparisons of baseline characteristics for daytime vs other shifts.

Response: In Table 1, we added *P*-values from Chi-square test comparing baseline characteristics across different nursing shifts.

3. Table 2: Should include in footnote a complete list of which variables were included in the final aOR models. Also, the analysis by day of week compared 6 days vs Monday as the referent, but without any adjustment for multiple hypothesis testing. Although plausible that the same issues might occur on Sunday rather than on other days of the week that occur on non-daytime shifts, this association is weaker than the main point and needs to be acknowledged. Should include a stricter threshold for inference testing for analysis by day of week.

Response: We added a complete list of adjusted variables in the footnote.

To address the multiple comparison issue, we used the Benjamini-Hochberg false discovery rate procedure [Ref] to adjust for *P*-values with the following steps:

1) Rank all of the *P*-values from the smallest to the largest.

- 2) Calculate a Q-value (adjusted P-value) for each P-value using the formula of (P-value multiply by the number of tests and then divided by the rank of that P-value).
- 3) Use a Q-value of 0.05 as the cutoff to select significant results. By using a Q-value of 0.05, we expect and can tolerate that 5% of the significant results will be false positives.

We marked the associations with adjusted P-value (Q-value) < 0.05 in Table 2. Also, in line 112 of the main text, we added the following sentence: "To address the potential of multiple comparisons, we used the Benjamini-Hochberg false discovery rate procedure to adjust for P-values [Ref]. We used an adjusted P-value of less than 0.05 as the threshold to select significant results."

[Ref] Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J Royal Stat Soc Series B (Method). 1995;57(1):289-300.

4. Table 3: Again, no adjustment for testing multiple hypotheses (36 in this Table) increases probability of some spurious associations, while also diluting the sample sizes so that there is less power to detect infrequent events.

Response: We used the Benjamini-Hochberg false discovery rate procedure as explained in the Statistical Editor's Comment #3 to adjust for multiple comparisons. We marked the associations with adjusted P-value < 0.05 in Table 3.

5. Fig 1 and Table 2: The odds ratios cited in Table 2 show an increase for evening and night shifts, while the right hand y-axis in Fig 1 A and B both show a decrease in odds. Need to clarify.

Response: The red line in Figure 1 A and B shows the odds ratio and it does show an increase for evening and night shifts.

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:

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

Please check with your coauthors to confirm that the disclosures listed in their eCTA forms are correctly disclosed on the manuscript's title page.

Response: correct disclosures confirmed

2. Was this study presented at the International Perinatal Collegium? If so, please disclose the name, date/s, and location of the meeting on the title page of your manuscript.

Response: We now enclose the above information on our title page.

3. 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..... Please write or insert the page numbers where each item appears in the margin of the checklist.

Response: our STROBE Form now has the pages where the requirements have been met

4. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative,....

Response: Our text is consistent with revitalize guidance

5. 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).

Response: Our Ms includes 19 pages and 2889 words

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

Response: our running title is now 40 characters including spaces

8. The most common deficiency in revised manuscripts involves the abstract

Response : Our abstract is consistent with the text. And has 275 words

13. The Journal's Production Editor had the following to say about this manuscript:

"Figure 1: Please upload as a high resolution figure file on Editorial Manager."

Response : a high resolution fig is now included