

OBSTETRICS & GYNECOLOGY



NOTICE: This document contains correspondence generated during peer review and subsequent revisions but before transmittal to production for composition and copyediting:

- 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: Sep 19, 2019
To: "Kendra Rene Sylvester-Armstrong" [REDACTED]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-19-1544

RE: Manuscript Number ONG-19-1544

Peripartum Stress-Dose Steroids: Necessary?

Dear Dr. Sylvester-Armstrong:

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 Oct 10, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

REVIEWER #1:

The authors review evidence related to whether there is benefit to administering stress-dose steroids in labor, a clinically-relevant and unresolved question. Comments and questions follow.

1. Current Practice. The paragraph mentions case reports and notes a lack of evidence. This might not need to be separate section. Lines 31-32 and 37-38 and 44-47 (which refer to 2 cases from the 1950's) don't provide much detail about the circumstances or applicability to obstetrics. Might present this content more fully and just 1 time.
2. Lines 42-43. Are there recommendations for or against use of stress-dose steroids in other surgical disciplines? Is there rationale for use in pregnancy if utility has not been demonstrated in other surgical (or medically stressful) situations outside of pregnancy?
3. Line 57-60. High-dose is defined as hydrocortisone 100 mg po q8 hrs. Low-dose is mentioned, so please define it as well.
4. Lines 68-74. What are the clinical implications of the hypercortisolism that characterizes normal pregnancy (in the setting of chronic steroid administration to treat a medical complication)?
5. Lines 75-76. Before trying to predict clinically relevant adrenal suppression during pregnancy, please describe how it would manifest and under what circumstances. More factual background content might be helpful for readers.
6. Lines 90-95 and 96-100. Please provide evidence that there is significant risk for these complications from a peripartum (1-day) course of steroids. The description seems excessive.
7. Lines 109-111. The authors write that in women without adrenal insufficiency who were treated with steroids chronically, there have been no cases of adrenal crisis. Please provide references for this statement, or if you conducted a Pubmed search, describe the search criteria. Here or elsewhere, please define chronic steroid use (how many weeks of treatment) and whether proximity to delivery (2nd vs 3rd trimester) matters.
8. Lines 118-120. Please clarify why obstetric hemorrhage and sepsis complicate the question of whether to administer stress-dose steroids.
9. Lines 126-130. The dosage and timing in this concluding recommendation were not introduced or discussed in the body

of the manuscript.

REVIEWER #2:

The authors present a clinical vignette and describe reports and studies to suggest that the practice of giving steroid treated patients "stress doses" during labor or Cesarean delivery, to prevent acute adrenal insufficiency, may not be warranted. In contrast to the notion that Cesarean delivery is more likely to be associated with an increased cortisol requirement, the authors cite a report demonstrating that the increase in serum cortisol was greater during labor and vaginal delivery than with elective Cesarean delivery.

The authors discuss potential risks of glucocorticoid therapy and conclude that clinically significant adrenal insufficiency is unlikely to occur if pregnant women do not receive stress doses of steroids during the intrapartum and postpartum periods.

The authors then provide some specific recommendations.

The authors challenge the long standing practice of giving pregnant patients [who are receiving therapeutic glucocorticoid therapy for a nonhypothalamic-pituitary-adrenal disorder] stress doses of steroids for labor and vaginal delivery and Cesarean delivery. This issue has been raised previously in the surgical literature; there is value for discussion of the merits of this practice in the obstetric patient.

Questions/Critique:

1-There is no discussion about a dose effect; can the authors expound on a the relationship between dose of exogenous corticosteroid and risk of adrenal suppression?

2-Do the authors feel that there are any peripartum conditions (i.e., lengthy labors and labor disorders, chorioamnionitis/intramniotic infection, preeclampsia, postpartum hemorrhage) that may place steroid treated patients at greater risk for acute adrenal insufficiency (and that have not been studied in available literature) and that merit consideration of stress doses?

3-The recommendations that are offered are a bit confusing and unclear. The first recommendation appears to be borrowed from the surgical literature and does not include the terms labor, vaginal delivery or Cesarean delivery. The second recommendation is for patients with an adrenal disorder who are on replacement doses of corticosteroids; although relevant this was not previously discussed in the manuscript and seems more straightforward in terms of its rationale - it does not need to be prefaced by the comment on absence of an RCT.

4. I think it would be helpful if the authors included in the section titled Current Practice - what are the existing current practice recommendations (duration, dose, and timing of steroid therapy that merits stress doses, recommended regimen of stress doses).

5. It would also be helpful if the recommendations are better clarified - specific recommendations for labor, vaginal delivery and Cesarean delivery (elective and unscheduled/emergent). If the recommendations are similar for all situations, this should be clearly specified. The authors might consider a reference for the dosaging recommended for stress coverage in the setting of a pre-existing adrenal disorder.

REVIEWER #3:

The authors are to be congratulated on their manuscript which calls into question the practice of "stress dose steroid administration" in pregnancy.

1) In addition to the recommendations set forth in this review and assessment of the literature, do the authors see any utility to a screening test of sorts (ie, ACTH stimulation test) to determine those patients who may be at risk and in whom the use of stress dose steroids may be more beneficial?

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. 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.

4. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Questioning Clinical Practice articles should not exceed 6 pages (1,500 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.

5. 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).

6. 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."

7. 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.

8. 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.

9. 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.

10. 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/ifauth.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 Oct 10, 2019, we will assume you wish to withdraw the manuscript from further consideration.

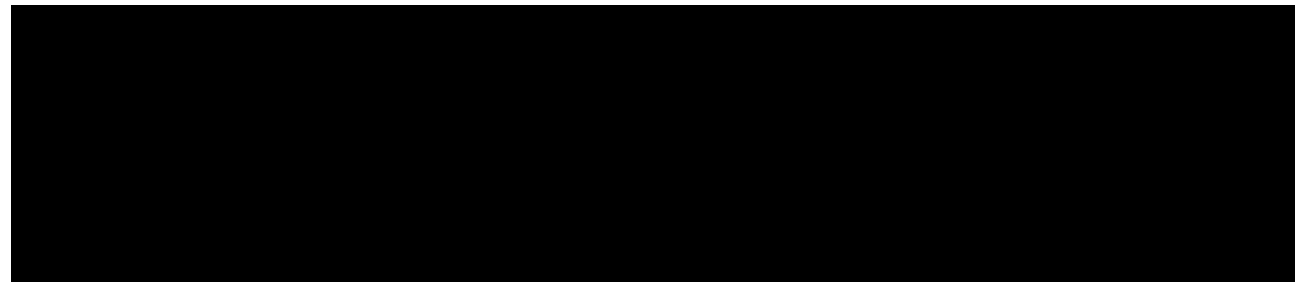
Sincerely,

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.



Nancy C. Chescheir, M.D.
Editor-in-Chief
Obstetrics and Gynecology Editorial Office
409 12th Street, SW
Washington, D.C. 20024

October 9, 2019

Dear Dr. Chescheir,

Please find enclosed the revised manuscript titled **“Peripartum Stress-Dose Steroids: Necessary?”** which we are re-submitting for your consideration for publication in the Green Journal in the Questioning Clinical Practice article as previously recommended by your editors. We have read the Instructions for Authors and included a point-by-point response to each of the received comments in the previous letter from the reviewers as instructed.

Our manuscript is original and is not under consideration elsewhere. All authors have read and approved the most recent version of the manuscript. The authors, Kendra R. Sylvester-Armstrong, M.D., W. Patrick Duff, M.D., and Mehmet R. Genç, M.D., Ph.D., have no conflicts of interest to report.

Sincerely,

Kendra R. Sylvester-Armstrong, MD



Responses to the reviewers

REVIEWER #1:

The authors review evidence related to whether there is benefit to administering stress-dose steroids in labor, a clinically-relevant and unresolved question. Comments and questions follow.

- 1. Current Practice. The paragraph mentions case reports and notes a lack of evidence. This might not need to be separate section. Lines 31-32 and 37-38 and 44-47 (which refer to 2 cases from the 1950's) don't provide much detail about the circumstances or applicability to obstetrics. Might present this content more fully and just 1 time.**

Separate Section – this section was included because it is required as one of the headings for the “questioning clinical practice” article submissions.

We agree with the above comments and revised the text accordingly (abridged version in manuscript). Here is our more detailed version from earlier version of the paper:

“Two case reports, each describing a single patient, gave rise to the above hypothesis. The first report² described a 34-year-old man with rheumatoid arthritis who was treated with cortisone, 25 mg twice daily, for 8 months. This medication was discontinued 2 days before hip arthroplasty. The patient developed hemodynamic collapse immediately following surgery and died. Autopsy showed bilateral adrenal atrophy, leading the authors to conclude that his death was due to acute adrenal insufficiency. The second case³ involved a 20-year-old woman, who also had rheumatoid arthritis treated with cortisone for 5 months prior to knee surgery. The patient developed hemodynamic instability progressing to death just 5 hours after surgery. Similar to the other case, the autopsy showed bilateral adrenal atrophy and hemorrhage. Over the next 6 decades, these case studies have been criticized for failing to account for several confounders, e.g., withholding of aggressive fluid resuscitation, vasopressors, and antibiotics, and, most importantly, for failing to provide subjective evidence of adrenal insufficiency, i.e., depressed serum cortisol.”

- 2. Lines 42-43. Are there recommendations for or against use of stress-dose steroids in other surgical disciplines? Is there rationale for use in pregnancy if utility has not been demonstrated in other surgical (or medically stressful) situations outside of pregnancy?**

As discussed in the manuscript, the use of stress dose steroid is controversial in any other surgical discipline. Although there is no proven rationale, it is a common practice in obstetrics and in other surgical situations. References 4-8 are listed for recommendations for and against its use in other surgical disciplines. Word limitations (<1500) did not allow to go into further detail of these papers, thus had to be excluded from the paper when the editors asked us to submit in this particular format.

- 
3. **Line 57-60. High-dose is defined as hydrocortisone 100 mg po q8 hrs. Low-dose is mentioned, so please define it as well.**

Low dose is mentioned in the text (line 65): intravenous hydrocortisone equivalent to presurgical oral dosing, followed by taper.

4. **Lines 68-74. What are the clinical implications of the hypercortisolism that characterizes normal pregnancy (in the setting of chronic steroid administration to treat a medical complication)?**

This was included in the original manuscript, however, secondary to word constraints, was left out of the final manuscript secondary to word constraint. Implied elsewhere in less detail in article in hopes that reader has this background information. If this needs to be included, we can shorten the following:

“Cortisol is essential for the maintenance of cardiac output and contractility and for enhancement of vascular tone and function. Transient increases of cortisol are seen in response to stress such as illness or surgery.¹ A common perception is that treatment with > 5 mg of prednisone/equivalent beyond three weeks may cause adrenal cortical atrophy. This effect, in turn, results in cortical suppression of ACTH production. Complete recovery of the HPA may take 12 months after glucocorticoid therapy has ceased. During this recovery time, the ability to increase cortisol production is limited, and in situations, such as surgery, where the need for cortisol is increased, such demand will not be met and, in turn, will lead to cardiovascular collapse.¹”

5. **Lines 75-76. Before trying to predict clinically relevant adrenal suppression during pregnancy, please describe how it would manifest and under what circumstances. More factual background content might be helpful for readers.**

100% agree. This description was taken out of original manuscript again for word constraint. Added to lines 87-93.

6. **Lines 90-95 and 96-100. Please provide evidence that there is significant risk for these complications from a peripartum (1-day) course of steroids. The description seems excessive.**

We agree with the comment and reviewed the available data on this issue.

7. **Lines 109-111. The authors write that in women without adrenal insufficiency who were treated with steroids chronically, there have been no cases of adrenal crisis. Please provide references for this statement, or if you conducted a Pubmed search, describe the search criteria. Here or elsewhere, please define chronic steroid use (how many weeks of treatment) and whether proximity to delivery (2nd vs 3rd trimester) matters.**

In a recent review article published in the European Journal of Endocrinology, a PubMed search was performed from published articles from 1976 onwards using keywords such as adrenal insufficiency, lactation and infertility. A detailed review of the literature was also completed. The search identified one literature review of 27 patients with secondary AI, none of which experienced adrenal crisis during their pregnancy. Since there are no reports on pregnant women, trimester specific data is not available. (reference 18)

8. Lines 118-120. Please clarify why obstetric hemorrhage and sepsis complicate the question of whether to administer stress-dose steroids.

We revised the text to clarify why it would be more difficult to link hypotension to adrenal insufficiency in obstetric patients with hemorrhage and sepsis.

9. Lines 126-130. The dosage and timing in this concluding recommendation were not introduced or discussed in the body of the manuscript.

10.

Endocrine society guidelines reference (19) is now included in body of manuscript.

REVIEWER #2:


1-There is no discussion about a dose effect; can the authors expound on the relationship between dose of exogenous corticosteroid and risk of adrenal suppression?

Such a relationship has not been reported for non-obstetric surgeries. For this reason we do not recommend any stress dose steroids for obstetric patients regardless of their maintenance dose or duration of treatment as stated in the text

2-Do the authors feel that there are any peripartum conditions (i.e., lengthy labors and labor disorders, chorioamnionitis/intramniotic infection, preeclampsia, postpartum hemorrhage) that may place steroid treated patients at greater risk for acute adrenal insufficiency (and that have not been studied in available literature) and that merit consideration of stress doses?

In the literature, there are no reports of adrenal insufficiency in obstetric patients with long-term steroid treatment. In non-obstetric surgical literature, there is no evidence that high-dose perioperative steroids prevented adverse outcomes in those with infection or increased blood loss.

3-The recommendations that are offered are a bit confusing and unclear. The first recommendation appears to be borrowed from the surgical literature and does not include the terms labor, vaginal delivery or Cesarean delivery. The second recommendation is for patients with an adrenal disorder who are on replacement doses of corticosteroids; although relevant this was not previously discussed in the



manuscript and seems more straightforward in terms of its rationale - it does not need to be prefaced by the comment on absence of an RCT.

The practice of the use of stress dose steroids was adopted by obstetricians from practices focusing on non-obstetric population. As stated in this communication, this practice which is not based on any evidence has any relevance for obstetric patients.

4. I think it would be helpful if the authors included in the section titled Current Practice - what are the existing current practice recommendations (duration, dose, and timing of steroid therapy that merits stress doses, recommended regimen of stress doses).

Included in new version of manuscript lines 151-155.

5. It would also be helpful if the recommendations are better clarified - specific recommendations for labor, vaginal delivery and Cesarean delivery (elective and unscheduled/emergent). If the recommendations are similar for all situations, this should be clearly specified. The authors might consider a reference for the dosaging recommended for stress coverage in the setting of a pre-existing adrenal disorder.

Clarified no specific recommendations, added to line 155-156.

REVIEWER #3:

The authors are to be congratulated on their manuscript which calls into question the practice of "stress dose steroid administration" in pregnancy.

- 1) In addition to the recommendations set forth in this review and assessment of the literature, do the authors see any utility to a screening test of sorts (ie, ACTH stimulation test) to determine those patients who may be at risk and in whom the use of stress dose steroids may be more beneficial?

Added line 108 - 112