OBSTETRICS & GYNECOLOGY

NOTICE: This document contains comments from the reviewers and editors generated during peer review of the initial manuscript submission and sent to the author via email.

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

Date: Nov 15, 2018
To: "Naomi K. Tepper" [REDACTED]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-18-1898

RE: Manuscript Number ONG-18-1898

Venous thromboembolism among women initiating depot medroxyprogesterone acetate immediately postpartum

Dear Dr. Tepper:

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 Dec 06, 2018, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1:

Overview: The authors present a population-based cohort study examining risk of venous thromboembolism after postpartum administration of medroxyprogesterone acetate. Findings include an increased risk of VTE compared to the population not using hormonal contraception. This is a well-reasoned and well-written study and a high priority area of research, given recent increasing emphasis on provision of immediate and early postpartum contraception.

Specific Comments:

1. Figure: It would be helpful to add the n in each category of the flow diagram.
2. The separate discussion of risk in women with and without VTE risk factors is helpful for clinical interpretation. Discussion of the finding that the DMPA group contained more women with risk factors would be helpful. This likely represents the long-held view (and recommendation) that DMPA is safer than other hormonal contraceptives in terms of VTE risk.
3. Comparison in the abstract and the discussion to the RR of VTE for women initiating estrogen-containing contraceptive methods would help to put this study in context (if known). Given the paucity of combined oral contraceptive safety data for comparison, the authors should emphasize what clinical implications these findings may have on postpartum contraceptive access in general. Access to DMPA and other progestins postpartum may be endangered unnecessarily should the study results be over-interpreted.
4. The last sentence of the discussion should be removed as it does not add to the manuscript. Consider suggesting a comparison of estrogen-containing pills and DMPA in the postpartum period (6-12 weeks) to delineate safety differences?

Reviewer #2:

Abstract:

Objective - To determine the absolute and relative risk of DVT with immediate DMPA use versus non-hormonal contraception

Methods - Database documenting delivery hospitalizations between 2005-2014, ages 15- 44 yo. Diagnosis, procedure, and drug does were collected to identify contraception, VTE, and potential confounders and pregnancy related conditions. Women receiving DMPA on days 0-7 postpartum were compared to those who did not and followed to 12 weeks for risk of VTE. Incidence rate and incidence rate ratio were evaluated.

Results - Unadjusted VTE risk through 12 weeks was 0.42/10,000 women-days versus 0.15 per 10,000 in women without hormonal contraception. Adjusting for age and pregnancy related conditions makes IRR 1.94 (1.38-2.72)

Conclusion - DMPA has a low incidence but increased RR to VTE compared to nonuse

Introduction - Immediate PP birth control with DMPA is commonly used as bridge to LARC but the concern is that there is an increased risk of thrombosis. DMPA has an 2-3 fold increased risk of VTE. The objective was to estimate the absolute and relative risk of VTE through 12 weeks with immediate PP DMPA compared to non-hormonal contraception.

Materials and Methods - Databases - linked information for inpatient, outpatient, and prescription drugs was evaluated

Cohort - women aged 15-44 who were hospitalized between 2005-2014

Exposures DMPA in first 7 d PP

Outcomes - VTE - DVT or PE by ICD-9 CM codes

Confounders - age, medical conditions that increase risk like CHTN, DM, obesity, smoking, and confounders - GHTN, multiple birth, GHTN, c-section, IUFD, infection, hemorrhage

Analysis - incidence rates VTE divided by women days , incidence rates and age-adjusted IRR evaluated

Results - 11,159 women with DMPA and 3 million who didn't receive DMPA group younger and more likely to have DM, CHTN, GHTN, preeclampsia, be obese, smoke

34 VTEs in the DMPA group versus 3107 in the group not receiving hormonal contraception

Discussion - DMPA is associated with an increased IRR for VTE but the absolute incidence rate is low - 0.42/10,000 versus 0.15 per 10,000.

Findings are similar to 2 smaller studies that show an increased risk of VTE.

The mechanisms are not well understood and limitations include misclassification of factors including obesity and smoking

Comments:

This paper is important since DMPA is thought to be safe for use for contraception PP and also in women with a history of VTE, so it is important to know if this is a misconception.

I do have a concern with data and confounders collected just by coding. There are risks - particularly obesity and smoking - that are not recorded as diagnoses and therefore not part of coding at all. Given that the DMPA group is such a small group in number as compared to the group that did not receive hormonal contraception, I am worried that a small number miscoded could affect the results with such a small margin of significance. I would be curious to know how many miscoded cases would have to exist for the findings with adjusted IRR to be no longer significant.

Why is women-days used rather than just distinct patients. Would a different denominator have affected the findings? how was this picked and why?

What is the possible mechanism - if DMPA is considered to be safe by the WHO MEC in women with h/o VTE, why is it not safe in PP women? This seems incongruous, so some discussion would be warranted.

The risk of VTE is slightly increased in DMPA users but the absolute risk is still so low, that I would be curious to compare that to the number of short interval pregnancies in users not obtaining contraception and the risk that is then incurred. This is obviously beyond the scope of the study, but some discussion of the risks in women with short pregnancy intervals should be included because perhaps with this, the DMPA is actually safer despite the risk of VTE.

Reviewer #3: The purpose of this study is to estimate the absolute and relative risk of venous thromboembolism among women who receive DMPA immediately postpartum compared with those who do not receive

Materials and Methods

You express that "The databases undergo quality assessments, including validity and reasonableness checks", which seems

to be a general assessment. Are there any validity / accuracy assessments for this study?

The comparison group should be more clearly defined. It is confusing and seems that this group includes women that may have initiated DMPA after seven days since the study or exposed group received DMPA day 0 - 7. Most likely, Table 3 compares an additional subgroup. This should be made clearer in the methods section.

Discussion Like any database study, the concerns are its limitations. These limitations are included in your discussion and the conclusions are justified.

STATISTICAL EDITOR COMMENTS:

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

Table 1: As pointed out by the Authors, the groups were different in many baseline factors which may have affected risk of VTE (DM, HTN, Obesity, smoking etc).

Table 2: To adjust for the differences at baseline, the Authors adjusted for 14 factors, yet there were only 34 cases of VTE among the DMPA group. This unfavorable proportion of adverse events to parameters is likely to have resulted in an over fitted model. The Authors need to supplement their analysis with a matching algorithm, using all the DMPA women, with closest match among the referent cohort. Since the latter had > 3.1 million women, that should be feasible with a resultant closely matched group which would then support or refute the association of VTE with DMPA.

Table 3: This analysis needs to include the number of VTE cases in each week. Given that the total was = 34, these subsets are likely too small to allow age adjustment. The small counts of adverse events has led to NS IRRs for several of these week intervals (wk 3, 5, 6), making generalization of these IRRs difficult.

EDITOR COMMENTS:

1. Thank you for your submission to Obstetrics & Gynecology. In addition to the comments from the reviewers above, you are being sent a notated PDF that contains the Editor's specific comments. Please review and consider the comments in this file prior to submitting your revised manuscript. These comments should be included in your point-by-point response cover letter.

The notated PDF is uploaded to this submission's record in Editorial Manager. If you cannot locate the file, contact Randi Zung and she will send it by email - rzung@greenjournal.org.

- The use of "women-days" instead of women is a bit of a problem. It is not intuitive about what that means for the doc in practice who counseling a woman in front of her or him. My strong preference would be that you present the data in terms of women rather than women days or at least provide it in addition to women-days. In particular, looking at women as the basis for analysis by week post partum. This will make your paper much more useful to the reader.

- Since this is something you are exploring in your paper--its safety in the post partum period would it be clearer to state "it is generally considered safe...."

- please limit p values to 3 decimal points

- we do not use the virgule (/) in the journal except in numerical expressions. Please edit here and throughout the paper.

- Perhaps. there were a total of 34 women who experienced VTE....

- These are very low rates of VTE. We published your paper in 2014 which used the same data base and the baseline rate reported was 9/10,000 also through 12 weeks. Why do you think you found such a low value? Now as I read this, I see you are reporting women-days as the unit, and that is the likely explanation. I agree with one reviewer who questions this choice. It is clearly not the typical way of doing this, and for counseling purposes is a bit less relevant than using women as the unit.

Obstet Gynecol. 2014 ; 123(5):987-96. Postpartum venous thromboembolism: incidence and risk factors. Tepper NK, Boulet SL, Whiteman MK, Monsour M, Marchbanks PA, Hooper WC, Curtis KM.

- so here you are talking about women, not women-days.

- although lower CS rate, which is also a risk factor.

- Do you think your conclusion should more firmly state that the absolute risk is still quite low, some would argue not clinically significantly different, and that use of this drug in the immediate post partum time period is a reasonable alternative to use of no reliable contraceptive in the immediate post partum period?

2. 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, as well as subsequent author queries. 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:

1. OPT-IN: Yes, please publish my response letter and subsequent email correspondence related to author queries.
2. OPT-OUT: No, please do not publish my response letter and subsequent email correspondence related to author queries.

3. Line 82: 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 Materials and Methods section, 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 web site outlining the exempt data sets or a letter from a representative of the IRB.

In addition, insert a sentence in the Materials and 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.

4. 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 will be transitioning as much as possible to use of the reVITALize definitions, and we encourage authors to familiarize themselves with them. The obstetric data definitions are available at <http://links.lww.com/AOG/A515>, and the gynecology data definitions are available at <http://links.lww.com/AOG/A935>.

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). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and appendixes).

Please limit your Introduction to 250 words and your Discussion to 750 words.

6. Specific rules govern the use of acknowledgments in the journal. Please edit your acknowledgments or provide more information in accordance with 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 signature on the journal's author agreement 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).

7. 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.

8. Only standard abbreviations and acronyms are allowed. A selected list is available online at <http://edmng.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.

9. 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.

10. 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.

11. Figure 1: Please consider adding n values.

12. If you choose to revise your manuscript, please submit your revision via Editorial Manager for Obstetrics & Gynecology at <http://ong.editorialmanager.com>. It is essential that your cover letter list point-by-point the changes made in response to each criticism. Also, please save and submit your manuscript in a word processing format such as Microsoft Word.

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

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 06, 2018, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Nancy C. Chescheir, MD
Editor-in-Chief

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

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