OBSTETRICS & GYNECOLOGY

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Date: Aug 28, 2018
To: "Mitchell D. Creinin" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-18-1392

RE: Manuscript Number ONG-18-1392

A U.S. Phase 3 study of a levonorgestrel 52 mg intrauterine system: five-year efficacy and safety

Dear Dr. Creinin:

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 Sep 18, 2018, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: Overall comments to author

Where is the data on effectiveness? You report on efficacy and safety, but not effectiveness. I am very curious about those lost to follow up. Not those who desire pregnancy (n=246) but those who withdrew consent, were lost to follow-up, or moved far from a study site (n=~360). These 360 account for about 1/3 of those who discontinued study participation. Can you make different assumptions about their pregnancy outcomes (experienced it at the same rate as the rest of the sample or experienced an expected probability of pregnancy based on other covariates or all experienced a pregnancy - obviously very unlikely but to provide a range of possible outcomes).

Do you have outcome data on those who discontinued due to perceived adverse events (n=324)?

In a similar vein, what about those who discontinued due to expulsion - do we know anything about them? Given that concerns about expulsion continue to drive practice and restrict access to IUS for some women (especially immediate post-partum) it would be nice to know what effectiveness looks like if we make some assumptions about outcomes for these n=65 women.

Abstract

1* Explicitly state this is a prospective cohort study?

2* In results - be explicit about the unit of analysis for Pearl Index and Life-table - to be sure everyone reading this can interpret the number? E.g. .15 pregnancies. This may seem really obvious but this paper needs to be understood by all and those could be misinterpreted as proportions or some other unit/metric

3* Line 53: "complain" I know this is routinely used in medicine, but if a patient reads this, she is not going to like that. Can you change to "report" here and throughout?

Intro

4* Line 68: "...IUS in 2000, and the single-rod implant in 2002" - add comma.

5* Thank you for succinct and clear Introduction

Methods

6* Line 95: add comma after "private offices". I leave it to the journal editors but the Oxford comma is easier to read.

7* Line 107: make clear that the 16-35 group is the efficacy study population. This comes up late but I don't think is mentioned in methods.

8* Lines 114-128: I got a bit lost in the study visits/follow-up. Would the following help flow and clarity:
a Lines 126-128 should come earlier ("thus participants…point between visits") - move up to Line 120, after "study visits". Then make a new paragraph and describe the diary.
b Lines 125-126: ("A follow up visit for urine pregnancy testing…after IUS discontinuation.") - move down after line 128: The study IUS could be removed whenever requested.

9* Were the IUS free? Were participants compensated? I realize this is on the prior publication but given what we know about LARC use when LARC is free it seems a relevant point to mention briefly.

10* Line 136: "…that month was included in the denominator but not in the numerator" - is that correct? Based on the previous sentence it seems so (and makes sense) but clarify in this sentence as well?

11* Line 139: will all readers (non-researchers) be familiar with the terms "life-table pregnancy rates" and "Kaplan-Meier method". They are both standard but at least provide a citation and consider adding a clause to help the reader interpret, e.g. "..Kaplan-Meier method, which produces x or allows us to see y". Clinicians reading this need to understand what is going on and feel confident interpreting the results. The best way to do that describe it without technical terms/jargon.

12* What about the discontinuations due to AE and study withdrawls - they contributed some data, could you simulate outcomes for them and include them as a sensitivity analysis? Simulate based on overall observed mean outcome, also depending on their covariates - those who withdraw are likely to be different than those who do not and that may affect probability of pregnancy. There are so many of them it would be ideal to use their data. This paper answers the efficacy question but effectiveness could also be addressed at least partially.

13* Describe stratified analysis - or perhaps if clarification of 16-35 as the efficacy sample is added (see above) that is enough. I was surprised to see all results stratified by age group, it was not set up in methods or I missed it.

Results

14* Table 1:
a Add footnotes to briefly describe Pearl Index and Life-Table pregnancy rate interpretation (e.g. # pregnancies/100 woman-years). I know it is in the text, but I'm thinking of when these tables are copied and pasted for presentations, and of readers who go straight to the tables.
b * for year 1, I got confused. A total of 3 pregnancies with 1 ectopic then (perf, expulsion, ectopic). Should it read "3 (1)" in the # pregnancies column? And why include this detail for year 1 but not the other years? I think I am missing something here.

15* Table 3: Provide total n/% of AEs resulting in discontinuation? It is in the text, but again, if readers skip to the tables…My brain went right to trying to add it all up. Could women have more than 1 reason or are these mutually exclusive?

16* Lines 167-171: I found the amenorrhea or spotting results very interesting and useful - is there a way to integrate it into Fig 2 in the main body of the text? Seeing the difference between amenorrhea and amenorrhea or spotting on the same graph would be nice. Even add the light bleeding? More data can easily be displayed on Fig 2 without it getting confusing.

17* Lines 183-185: It was not clear to me how inclusion of sentence about the n=579 (33%) who discontinued for product-related reasons or desiring pregnancy was useful. Above this, you list all the reasons women discontinued IUS and/or left the study. If you want to keep this sentence, move it up as an introduction to the more detailed numbers you present. It felt odd to scope out again at the end of the paragraph. My brain got distracted trying to make all the numbers add up.

18* Line 188: here is the AE data my brain was trying to add up looking at Table 2. Sometimes it is worth repeating data so that both text and tables can stand alone.

19* Line 196: ditto - overall n/% who discontinued due to AE - add to table 3.

Discussion

20* I was struck by the lack of any mention or discussion of Mirena - how do these new Liletta 5 year data compare with what we know about Mirena 5 year data? (I use trade names as shorthand and realize you may not want to/be able to). It seems like readers will want to know how your results compare with other similar (if not identical) products in terms of efficacy and safety. A clinician who wants to counsel a patient about 5 year efficacy using your paper will have to go look

up a Mirena paper to do so, unless s/he has those number burned into her/his brain (which is possible).

21* Check that refs 11, 12, 13 are in order - perhaps 11 & 12 (lines 237) are cited earlier in the text, but seems like they follow #13 (line 226).

Reviewer #2: This study is 5 year follow-up of new LNG IUS device. Study developed, paid for, oversaw by one of pharmaceutical companies manufacturing device. Authors do not include an objective or aim of study in the paper. Only objective is in the abstract and is broad - "safety and efficacy." Paper lacks detailed demographic information about study population. Limitations include high discontinuation rates over time of IUS (68% at 5 years) and low number of participants in 36-45 yo group (8.5% of all participants). It would strengthen paper to include information about how this IUS compares to other IUS and LARC devices in terms of pregnancy rates, adverse events, discontinuation rates, etc.

1. Line 81-82 -which year is this data from and please define by $$ amount what is 200% below poverty level and what % of women fall into this category?

2. Line 84 - how does developing a new IUS address barriers to contraception describes in paper? Please provide detail here as simply adding a new product to the market does not guarantee increased accessibility with described barriers

3. Line 87-88 - this is not an objective or aim of the paper. Objective or aim required in the body of the paper

4. Line 96-97 - please explain "as applicable"

5. Line 100-107 - how were women recruited? What were exclusion criteria, other inclusion criteria?

6. Line 118-120 -what questions were asked in phone interviews? If participants were not required to check for the IUS string (line 111-113), how did they confirm IUS in place at phone interviews?

7. Line 120-123 - why were diary questions and information changed after 24 months?

8. Line 125 - please define or explain what is meant by "safety assessments" here

9. Line 129-130- please clarify this statement and provide more detailed information. How can authors assess pregnancy outcomes at 5 years with only one follow-up contact? What was the time frame for this one contact? 60 months? Or were medical records examined?

10. Line 140-141 - if paper looking at 5 years for safety and efficacy, why include 8 years for results? This should be limited to 5 years and broken out by year if included all participants, not just those who used IUS for 5 years.

11. Line 142-145 - references here please

12. Line 155-159 and figure 1 - why such low rates of study participants (146 patients) in 36-45 yo group? This is only 8.5% of all study participants at the start.

13. Line 167-169 - please rephrase as this sentence is confusing as written

14. Line 171-175 -what were the bleeding amounts and severity of cramping in the rest of participants?

15. Line 177 - why such small numbers of participants continuing use at 6-8 years?

16. Line 216 - please define what is included in "hormonal" adverse event here

17. Line 221-231- what was the % obese women in this study and results for these two groups years 1-3? What is % of these 2 groups at years 3-5 of study? Please provide more detail here.

18. Line 238-244 - please define "clinically apparent"

19. Line 245-248 - given the large disparity in size between these two groups, hard to assess differences in age with use. Larger group of 36-45 yo needed.

Reviewer #3: This is an important study reporting on efficacy and safety of a low cost 52mg LNG IUS, 5 years for efficacy data and up to 7 years for safety. The study had broad inclusion criteria with a large percentage of nulliparous participants and obese women which reflects many current IUD users. Pregnancy rates were low through five years. Adverse event data is presented in several important ways, by age, by event type and by discontinuation rate which is helpful for clinicians counseling patients before and after LNG IUS insertion.

STROBE checklist is included with lines cited and IRB approval/clinical trial number is indicated. No conflicts of interest are

noted.

ABSTRACT:

The objective and methods are clear. It may be helpful to indicate in the methods that this novel IUS is Liletta as some generalist readers may not be aware of the device

Results: Consider presenting percentage with numerator and denominator in lines 49, 55, 55 and 57 to orient the reader. Did you perform statistical testing to determine that adverse events differed significantly by age, if so include relevant p value in line 55. If space allows, it may be helpful to indicate that pelvic infection included only endometritis or PID diagnosed by a clinician.

PRECIS: Clear.

INTRODUCTION:
Clearly defines the importance of LARC use in reducing unintended pregnancy rates, the barriers to uptake of cost and why the device/trial was designed.

MATERIALS AND METHODS:
This is clear and provides reference to prior publications where the study methodology is fully detailed but enough information is presented to here for readers to understand inclusion criteria, how study was performed and how pregnancy outcomes and adverse events were collected and reported.

RESULTS: In line 156, consider presenting the percentage of women ages 16-35 and women ages 36-45 to provide better context for clinicians. In line 162, was this difference in pregnancy rates between nulliparous and parous women statistically different? In lines 210-212 which discuss ovarian cysts, was ultrasound of the adnexa done routinely as part of the study? Is there any information about percentage of women who were symptomatic with ovarian cysts? This information would be helpful for the argument made in lines 242-244.

DISCUSSION: In line 216, the term "hormonal adverse events" is confusing, this includes bleeding only or any of the non-expulsion adverse events in table 3?

Figure and tables have clear titles and are understandable.

STATISTICAL EDITOR'S COMMENTS:

1. lines 48-56: Need to include a concise summary of how many women (%) completed 5 years.

2. lines 55-59, 140-142 and Tables 2,3: The proportions cited for adverse events used the entire original cohort as the denominator, but the number still included in the study decreased over time. Shouldn't a better (time-dependent) metric be used to cite the rates of adverse events? For instance, how can expulsion rates be based on a denominator comprised of women with and without an IUD?

3. Table 3, Fig 1: The differential continuation rates (34% of younger cohort vs 60% of older one at 5 years), also biases these rates. Comparisons are also limited by the low counts among the smaller cohort, which limits power. Therefore, cannot generalize the NS findings of comparisons by age cohort.

4. Fig 2: Should include CIs for the bar graphs.

ASSOC EDITOR-GYN

1 - Please elaborate in Methods on the role of Medicines360 beyond the single sentence line 97-98: presumably it provided all funding, etc

2 - Please provide in Methods a statement regarding whether the investigators followed the guidelines of good pharamacoepidemiology practice (GPP)?

EDITORIAL OFFICE COMMENTS:

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1. OPT-IN: Yes, please publish my response letter and subsequent email correspondence related to author queries.
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2. 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.

3. 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.

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

"Figure 1: In the 36–45 years of age group, please confirm the n values for the first 4 boxes (151-25=126)"

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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 Sep 18, 2018, we will assume you wish to withdraw the manuscript from further consideration.

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The Editors of Obstetrics & Gynecology

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