

OBSTETRICS & GYNECOLOGY



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

Date: Dec 06, 2019
To: "David K. Turok" [REDACTED]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-19-2024

RE: Manuscript Number ONG-19-2024

Efficacy, safety, and tolerability of a new low-dose copper and nitinol intrauterine device: Phase 2 data to 36-months

Dear Dr. Turok:

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 27, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: Authors

Abstract

1. What is US MEC?

Intro

2. How does this IUD compare to IUDs on the market worldwide? CU SAFE 300 IUD? What would be its advantages over what's already available (i.e. why does another new copper IUD need to be created vs. bringing what's already on the market to US)?

3. Is phase 1 study published? I was only able to locate an abstract below in Contraception in 2014 but no paper.

Reeves M, Katz B, Canela J, Hathaway M, Tal M. Initial evaluation of a novel nitinol, low-dose-copper intrauterine contraceptive. Contraception 2014;90:315.

4. For those not familiar with nitinol, why is it used in contraceptive devices?

5. Lines 93-99

How do dimensions and inserted compare to T380A, and to current IUDs on the market in US (Skyla, Kyleena, etc)? What size matter in terms of ease of insertion for smaller uterus/nulliparous uterus?

6. Would precut string length be a problem in large cavity? Immediate post-placental insertion, or large fibroid uterus? In those cases, leaving strings long and cutting them short later at another visit is an advantage

Methods

7. Pearl index vs. life tables.

Separating women into younger/older (ie more and less likely to get pregnant) is of help. Life table more useful than Pearl index, but good to have info about both.

8. Is it possible to know how many women took or were told to take NSAIDS for bleeding/cramping? It is common practice to do that with copper T, so is that something that occurred in this study?

9. Were subjects paid to participate?

10. Was the sample size set by FDA phase 2 requirements or some other considerations? My understanding FDA sets those numbers, but please explain for general audience

Results

11. Bleeding days decreased over time.

Is that comparable with trends of other non-hormonal IUDs?

12. How does efficacy, ease of placement, and discontinuation rates data compare to other IUDs?

13. In table 3, dysmenorrhea and pain AI are high. Is there any more detail avail on that, along with post-procedural hemorrhage?

14. Fig 1

Looking at IUD picture, is there risk of arms/copper sleeves getting stuck in myometrium in case of partial perf resulting in embedded IUD? Those are hard to get out as arms break off and get stuck in existing iuds, but his seems like it would be even more problematic.

Discussion

15. Has this IUD been studies elsewhere aside from ref 2?

Reviewer #2: Overview: This manuscript describes 36-month data of a novel low-dose copper-nitinol IUD. Authors found high efficacy and tolerability, however a lack of included detail limits understanding of generalizability. I recommend the following revisions to improve the clarity and quality of the manuscript:

1. Title and Abstract: The title and abstract appropriately reflect the manuscript. Because the primary outcome was the 12-month Pearl Index, this should also be included in the abstract.

Page 6, line 84: "deceased" should be "decreased"

2. Introduction: The introduction clearly describes the reasoning for this study. Can delete sentence in lines 99-100 as it is redundant. Sentence in line 103-104 is incomplete (possibly: the copper-nitinol IUD was associated with lower pain scores).

3. Methods:

Role of Funding Source: more detail is required here, such as in this recent Green Journal article "Concordance of Fingerstick and Venipuncture Sampling for Fertility Hormones" February 2019. Alternately, a more concise version such as in "Patterns of Prescription Opioid Use in Women With Endometriosis: Evaluating Prolonged Use, Daily Dose, and Concomitant Use With Benzodiazepines" June 2019. Detail should be included in this section rather than throughout the manuscript.

Line 125-126: Did all participants agree to participate in the 2-year extension?

Line 132: change "last 3 months" to "3 months prior to enrollment"

Line 147: cite ASCCP guidelines

Line 150: include actual citation here

Line 151-152: what is "prescribed placement" of IUD?

Line 154: If IUD placement was not fundal, what was done?

4. Results:

Why were the 131 screened participants not eligible? Please include either in text or Figure 2.

Line 218: were all 286 enrolled participants tested at time of insertion?

Paragraph lines 223-230 discusses low rate of discontinuation due to pain/bleeding, however only 37.8% of participants continued use to 36 months. Please include whether this discrepancy is due to LTFU or discontinuation for other reasons. Also include rate of discontinuation due to desire for pregnancy. Bleeding days are included in abstract but not in results.

Line 222: What percentage of cycles were the "assumed evaluable" rather than assessed directly?

Line 232: it seems as if the ectopic pregnancy is likely related to the study device as this is a known risk of FDA-approved IUDs.

Were age or parity associated with discontinuation?

Figure 1: please also include a diagram of the inserter.

Figure 2: remove text that states "PLACEHOLDER"

5. Discussion: Inappropriate comparison to LNG IUD data. Consider citation for T380 comparison or including data for other smaller copper IUD such as Mona Lisa.

6. References: Include copper IUD comparator as noted in Discussion comment.

Reviewer #3: Easy to understand summary of Phase 2 trial for novel copper IUD. Exciting to see another non-hormonal contraceptive method moving closer to approval

A few questions:

What's the intended duration of use for this new IUD? I understand this study was for three years but is the intention to continue to collect data beyond that time? Were the patients all instructed to have the IUD removed at the end of 3 years?

It might be helpful to tell readers what nitinol is made of.

Lastly, African Americans are over-represented in the study (as compared to the percentage in the general population) and I'm wondering if you might comment on why that is. I think this is an especially important consideration in light of LARC coercion in previous contraceptive studies.

STATISTICAL EDITOR'S COMMENTS:

1. Abstract: Should include median (range) time for continuation and rate (or hazard rate) for discontinuation.
2. Table 1: For the column of 36-40 yo, the N = 25, so all percentages should be rounded to nearest integer, rather than citing to 0.1% precision.
3. Table 3: Should include CIs for the AE proportions.
4. Fig 3: The labels for K-M curves appear to have been reversed, with the subjects with device expulsion have essentially 100% continuation rates. Should include the "N" remaining in each cohort at the time increments along the x-axis.

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:

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

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(1) Adherence to the GPP3 guideline should be noted in the cover letter.

(2) For publication purposes, the portions of particular importance to industry-sponsored research are below. In your cover letter, please indicate whether the following statements are true or false, and provide an explanation if necessary:

(2a) All authors had access to relevant aggregated study data and other information (for example, the study protocol) required to understand and report research findings.

(2b) All authors take responsibility for the way in which research findings are presented and published, were fully involved at all stages of publication and presentation development and are willing to take public responsibility for all aspects of the work.

(2c) The author list accurately reflects all substantial intellectual contributions to the research, data analyses, and publication or presentation development. Relevant contributions from persons who did not qualify as authors are disclosed in the acknowledgments.

(2d) The role of the sponsor in the design, execution, analysis, reporting, and funding (if applicable) of the research has been fully disclosed in all publications and presentations of the findings. Any involvement by persons or organizations with an interest (financial or nonfinancial) in the findings has also been disclosed.

(2e) All authors have disclosed any relationships or potential competing interests relating to the research and its publication or presentation.

(3) The abstract should contain an additional heading, "Funding Source," and should provide an abbreviated listing of the funder(s).

(4) In the manuscript, a new heading—"Role of the Funding Source"—should be inserted before the Methods and contain a detailed description of the sponsor's role as well as the following language:

"The authors had access to relevant aggregated study data and other information (such as study protocol, analytic plan and report, validated data table, and clinical study report) required to understand and report research findings. The authors take responsibility for the presentation and publication of the research findings, have been fully involved at all stages of publication and presentation development, and are willing to take public responsibility for all aspects of the work. All individuals included as authors and contributors who made substantial intellectual contributions to the research, data analysis, and publication or presentation development are listed appropriately. The role of the sponsor in the design, execution, analysis, reporting, and funding is fully disclosed. The authors' personal interests, financial or non-financial, relating to this research and its publication have been disclosed." Authors should only include the above statement if all of it is true, and they should attest to this in the cover letter (see #2, above).

*From Battisti WP, Wager E, Baltzer L, Bridges D, Cairns A, Carswell CI, et al. Good publication practice for communicating company-sponsored medical research: GPP3. *Ann Intern Med* 2015;163:461-4.

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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.

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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.

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12. 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%).

13. 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.

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- * 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 Dec 27, 2019, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

The Editors of Obstetrics & Gynecology

2018 IMPACT FACTOR: 4.965

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