

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.*

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obgyn@greenjournal.org.

Date: Aug 05, 2019
To: "Alyssa Covelli Colwill" [REDACTED]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-19-1155

RE: Manuscript Number ONG-19-1155

Opioid Analgesia for Medical Abortion: A Randomized Controlled Trial

Dear Dr. Colwill:

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 Aug 26, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: This is a well-designed randomized double-blind, placebo-controlled trial examining the role of a potent opioid in reducing pain experienced during medical abortion. A strong opioid given at the time of cramping did not reduce overall pain or number of subsequent opioids used. This adds to existent literature that we overprescribe opioids in gynecology but is unique in that it specifically addresses medical abortion.

How did you arrive at the marijuana exclusion criteria?

The sentence on line 182 is awkward and needs to be reworded.

I would like to see more recommendations in your discussion. For example, experienced pain strongly correlated with anticipatory pain. Do you think there is anything that we could do with that information? Why prescribe any opioids or individualize based on anticipated pain?

As many providers do not provide medical abortions, I think it is still important to mention that providers could consider this when utilizing medical management for failed intrauterine pregnancies although this study did not specifically address that particular scenario.

Reviewer #2: "Opioid Analgesia for Medical Abortion: A Randomized Controlled Trial" is a randomized, double-blind, placebo-controlled trial with the primary objective of estimating the effect of oral opioids on patient pain during first-trimester. This is a timely, well written, and important study. It is both relevant from an abortion access standpoint, as medication abortion is increasingly common in some areas of the country due to restrictions placed on free standing surgical abortion clinics as well as providing evidence based prescribing patterns that are lacking in our current opioid crisis. I have the following comments and queries:

1. Line 130: Were instructions for oxycodone/ placebo use offered in the patient's primary language? If not, do you think this contributed to the multiple deviations from the study protocol?
2. Line 210: I would also suggest that a strength of this study is that it focuses on medication abortions. On review of this literature I found few comparable studies looking at opioid analgesia at the time of abortion and they pertained to surgical procedures.

3. Line 229: Please further explain why you suggest prescribing opioids in some circumstances when you have clearly shown that oxycodone does not reduce the amount or duration of maximum pain experienced or the duration of overall pain in women undergoing medical abortion.

Reviewer #3: This is a randomized controlled trial comparing oxycodone 10 mg versus placebo taken at the onset of cramping on maximum pain within 24 hours post-misoprostol in women undergoing first trimester medical abortion. The authors found no difference in max pain between the two treatment groups. Overall, this study is well-done and relevant to those who provide medical abortions to understand how much narcotics are being used and to adjust their prescribing patterns.

Abstract:

1. Line 30: When was the text message sent within the 24 hour period after misoprostol?
2. Line 33: Satisfaction with what? Pain control?
3. Lines 38-9: For the mean duration of maximum pain, the SD is larger than the mean given, which suggests that the distribution is not normal. I recommend re-analyzing using the median duration of maximum pain instead.
4. Line 44: "or other outcomes" is vague. I would specify what the outcomes are.

Introduction

1. The introduction is succinct and provides sufficient background to highlight the compelling reasons to perform this study. Consider adding in references for variations in physician prescribing patterns (Guilbert ER Can Fam Physician 2016; Fiala C Eur J Obstet Gynecol Reprod Biol 2018).

Methods

1. The primary outcome and secondary outcomes are not clearly stated in the methods section.
2. Lines 117-8: The authors state that to allow for 10% drop-out, they planned to enroll 38 participants per group for a total of 152 participants. It appears that the authors are also stratifying by gestational age, can the authors clarify this in the text?
3. Which statistical analysis tests did the authors use? It is not included in the text or in the tables.

Results

1. Did anyone require more than the 6 adjunctive oxycodone tablets? How were the participants instructed to use the oxycodone (e.g. 1 tab every 2 hours?)
2. Lines 178 on: Typically the outcome of "successful medical abortion" is defined as passage of pregnancy without need for surgical intervention. Therefore, those participants who completed with another dose of misoprostol and with expectant management wouldn't be counted as a "unsuccessful". Since the secondary outcomes are not specified in the methods, it's unclear what the authors are trying to show with these results (safety of med abortion? Pain difference for the 3 ongoing vs not?) The numbers are so small in this group that it doesn't seem relevant to do many comparisons with the "successful" group.
3. Overall, the results section is 2.5 pages long. Much of the info presented in the text is also in the tables. Can the authors streamline the results section to avoid reader fatigue?

Discussion

1. Do the authors have enough info from the placebo group to describe what the usual pain course is for patients undergoing medical abortion?

Figures/Tables

1. Figure 1- For the screen fail (n=10), can the authors describe what the "other" is since there is only 1 participant in this group? The numbers don't add up for "allocated to placebo" under gestational age <7 weeks and "allocated to oxycodone" under gestational age 7-10 weeks. How many people completed the 6 hour text message and the 24 hour text message? When was the primary outcome determined?

STATISTICAL EDITOR COMMENTS:

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

lines 30-31, 36-39, 110-120: Need to separate the (1) primary outcome from all the others (including subset by GA), those are secondary outcomes, were not factored into the power/sample size calculation. None of the secondary outcomes that were NS can be generalized, since they were not primary.

Table 1: If any participant characteristics had been statistically different, then that is thought to be due to random chance, since the cohorts were randomly chosen. No need to include column of stats.

Table 2 and Fig 1: Per the flow diagram, there were 2 patients lost to follow-up before the 6h and 24h measures of pain score. Therefore, how can there be 86 +86 patients available for the primary outcome (and others) as cited in Table 2? Also, the primary outcome was max pain score, not duration of pain score or proportion having pain scores > 7, etc. Need to clearly separate the primary outcome from all the others, they were secondary.

Table 3: This analysis by subset was not factored into the primary power/sample size analysis, has lower counts than the aggregate and should not be labelled as a primary outcome. If it had been, then the initial inference threshold would have to have been $p < .017$, rather than the $p < .05$ inference threshold for 1 primary outcome. Since these comparisons were under powered, none of the NS findings can be generalized.

Fig 1: What were the baseline characteristics of the 75+5=80 women who either declined or were not included due to staff unavailable? That is, was the final randomized cohort representative of all the women who would have been eligible?

Fig 1 and Supplemental material: Since there were 49 women (~ 28%) who did not take the allocated intervention, the per protocol analysis should be included in the main text, not in supplemental, (at least that portion related to the primary outcome.)

Also in supplemental: Rather than (app 3), comparing the participant characteristics of Oxy vs placebo in the PP analysis, should compare the PP subsets vs those who were randomized, but then were allocated to a different treatment, in order to determine whether those who were allocated to the different treatment differed in ways that might affect the analysis of the max pain scores.

EDITOR COMMENTS:

1. Thank you for your submission to Obstetrics & Gynecology. Your paper is very well written. Please pay particular attention to the Statistical Editor's points as these must be addressed clearly. 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.

- 18 years

- We prefer to avoid providing p values only unless that is the only appropriate test of significance. Where possible in the abstract AND the text, please provide an effect size (such as an OR or RR) and 95% CI's.

- how about "by 99.4%"?

- We do not allow authors to describe variables or outcomes in terms that imply a difference (such as the terms "trend" or "tendency" or "marginally different") unless there is a statistical difference. Please edit here and throughout.

- Is this rate typical for medical abortion?

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. 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.

3. 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.

4. Clinical trials submitted to the journal as of July 1, 2018, must include a data sharing statement. The statement should indicate 1) whether individual deidentified participant data (including data dictionaries) will be shared; 2) what data in particular will be shared; 3) whether additional, related documents will be available (eg, study protocol, statistical analysis plan, etc.); 4) when the data will become available and for how long; and 5) by what access criteria data will be shared (including with whom, for what types of analyses, and by what mechanism). Responses to the five bullet points should be provided in a box at the end of the article (after the References section).

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. 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).

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

9. 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."

10. 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.

11. Abstracts for all randomized, controlled trials should be structured according to the journal's standard format. The Methods section should include the primary outcome and sample size justification. The Results section should begin with the dates of enrollment to the study, a description of demographics, and the primary outcome analysis. Please review the sample abstract that is located online here: http://edmgr.ovid.com/ong/accounts/sampleabstract_RCT.pdf. Please edit your abstract as needed.

12. 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.

13. 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.

14. 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%).

15. 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.

16. The American College of Obstetricians and Gynecologists' (ACOG) documents are frequently updated. These documents may be withdrawn and replaced with newer, revised versions. If you cite ACOG documents in your manuscript, be sure the reference you are citing is still current and available. If the reference you are citing has been updated (ie, replaced by a newer version), please ensure that the new version supports whatever statement you are making in your manuscript and then update your reference list accordingly (exceptions could include manuscripts that address items of historical interest). If the reference you are citing has been withdrawn with no clear replacement, please contact the editorial office for assistance (obgyn@greenjournal.org). In most cases, if an ACOG document has been withdrawn, it should not be referenced in your manuscript (exceptions could include manuscripts that address items of historical interest). All ACOG documents (eg, Committee Opinions and Practice Bulletins) may be found via the Clinical Guidance & Publications page at <https://www.acog.org/Clinical-Guidance-and-Publications/Search-Clinical-Guidance>.

17. Figure 1: Please confirm or explain n values for those allocated to placebo for <7 weeks (34+13=47) and those allocated to oxycodone for 7-10 weeks (24+13=37).

18. To ensure a quality experience for those viewing supplemental digital content, the journal's publisher suggests that authors submit supplemental digital files no larger than 10 MB each. The exceptions to this rule are audio or video files, which are acceptable up to 100 MB. When submitting text files or tables as supplemental digital content with your revisions, please do not submit PDFs.

19. 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.

20. 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 Aug 26, 2019, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Nancy C. Chescheir, MD
Editor-in-Chief

2018 IMPACT FACTOR: 4.965
2018 IMPACT FACTOR RANKING: 7th out of 83 ob/gyn journals

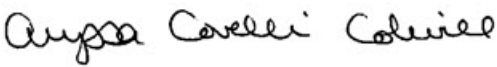
In compliance with data protection regulations, you may request that we remove your personal registration details at any time. (Use the following URL: <https://www.editorialmanager.com/ong/login.asp?a=r>). Please contact the publication office if you have any questions.



Dear Dr. Nancy Chescheir:

We are resubmitting our article, "Opioid Analgesia for Medical Abortion: A Randomized Controlled Trial" for consideration of publication in *Obstetrics & Gynecology*. The data has never been published and is solely submitted to *Obstetrics & Gynecology*. The manuscript is not under consideration elsewhere, and will not be submitted elsewhere until a final decision is made by the Editors of *Obstetrics & Gynecology*.

The lead author* affirms that this 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 (and, if relevant, registered) have been explained.

Signed by: 

***The manuscript's guarantor.**

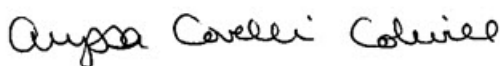
This trial was registered and the protocol reporting to *Obstetrics & Gynecology* is identical to the posted trial. Clinical trial registration: ClinicalTrials.gov, NCT03139240

We received IRB approval for the study. The authors have fulfilled the following criteria: disclosing potential conflicts of interest, acknowledging our funder, and disclosing conflicts of interest in the title page of our manuscript. The CONSORT guidelines were followed in writing this manuscript. The CONSORT 2010 Checklist was submitted with the manuscript. Word count for each section is as follows: abstract 298, introduction 251, materials and methods 907, results 746, discussion 762, manuscript 2964.

Please see our responses to the editor and reviewers below.

We look forward to hearing from you.

Sincerely,



Alyssa Covelli Colwill, MD, MCR

[REDACTED]

REVIEWER COMMENTS:

Reviewer #1: This is a well-designed randomized double-blind, placebo-controlled trial examining the role of a potent opioid in reducing pain experienced during medical abortion. A strong opioid given at the time of cramping did not reduce overall pain or number of subsequent opioids used. This adds to existent literature that we overprescribe opioids in gynecology but is unique in that it specifically addresses medical abortion.

1. How did you arrive at the marijuana exclusion criteria?

Marijuana is legal both recreationally and medically in the state of Oregon where this study was conducted. There is evidence that marijuana reduces perceived pain and reduces the need for opioids (O'Connell M et al., Medical Cannabis: Effects on Opioid and Benzodiazepine Requirements for Pain Control. *Ann Pharmacother*. 2019 May 25). Women do use marijuana for medical abortion-related pain (Louie, K., et al., *A survey study of marijuana use for pain management during first-trimester medical abortion*. *Contraception*. **94**(4): p. 394). We wanted a population that was representative for the entire country, of which most states do not have this broader access to and more accepted use of marijuana.

2. The sentence on line 182 is awkward and needs to be reworded.

We agree this line was awkward. Additionally after completing further edits, we did not find this sentence to be significant since there were such small numbers that were being compared. We deleted this sentence all together.

3. I would like to see more recommendations in your discussion. For example, experienced pain strongly correlated with anticipatory pain. Do you think there is anything that we could do with that information? Why prescribe any opioids or individualize based on anticipated pain?

We have tried to clarify our recommendations in the discussion section that are supported by our findings. Our exclusion criteria limits the generalizability of our results for women who may have experienced pain differently like former or current illicit drug user or women with chronic pain disorders. Additionally, women who have high anticipated pain may benefit from the knowing they have a prescription for adjuvant pain medication. Our final recommendation is that if opioids are offered, they should be provided a limited prescription. We have added the following to lines:

Lines 279-289: "Women who enrolled had to be accepting of the possibility of using an opioid and be opioid naive, which may skew the population towards women who are fearful of pain and more likely to use opioids. Our exclusion criteria limits the generalizability of our results for women who may experience pain differently like those that have or are using illicit drugs, chronic opioids, or women with chronic pain disorders. A subject's anticipated pain did strongly correlate with experienced pain. Therefore, it would be reasonable to use this information to determine whether to offer additional therapies to aid in pain control on an individual patient basis."

However, we found that opioids in our study did not improve pain, yielding us to recommend that routine prescribing of opioids is unnecessary. Lines 294-296: "We can conclude that routinely prescribing opioids for medical abortion up to 10 0/7 weeks is unnecessary but if opioids are requested, we would recommend providing 4 tablets or less."

4. As many providers do not provide medical abortions, I think it is still important to mention that providers could consider this when utilizing medical management for failed intrauterine pregnancies although this study did not specifically address that particular scenario.

We agree given the similarities in the experience of pain around medical management of miscarriage that our findings can be extrapolated. We have added the following information to lines 287-289: "While we did not study pain management for medical management of early pregnancy loss, we believe given the similarities in the pain experience that it is reasonable to extrapolate our study findings to this patient population as well."

Reviewer #2: "Opioid Analgesia for Medical Abortion: A Randomized Controlled Trial" is a randomized, double-blind, placebo-controlled trial with the primary objective of estimating the effect of oral opioids on patient pain during first-trimester. This is a timely, well written, and important study. It is both relevant from an abortion access standpoint, as medication abortion is increasingly common in some areas of the country due to restrictions placed on free standing surgical abortion clinics as well as providing evidence based prescribing patterns that are lacking in our current opioid crisis. I have the following comments and queries:

1. Line 130: Were instructions for oxycodone/ placebo use offered in the patient's primary language? If not, do you think this contributed to the multiple deviations from the study protocol?

We provided instructions verbally and written in the patient's primary language and had them equivalent to a grade 8 level. In order to be included in the study, women needed to be literate in English to participate in the study since the study materials and text message platform was only available in English. This eligibility criteria is listed in line 100. We do not believe this contributed to the multiple deviations in the study protocol. Our conclusion is that lower reported pain scores in this group implied pain was not severe enough to need additional opioids beyond ibuprofen (lines 250-258).

2. Line 210: I would also suggest that a strength of this study is that it focuses on mediation abortions. On review of this literature I found few comparable studies looking at opioid analgesia at the time of abortion and they pertained to surgical procedures.

That was one of our main motivators to design and perform this study. We have added a sentence in the discussion section line 267-269 in order to highlight this: "Our study is the only one to date that examines the effect of opioid use for medical abortion using the current recommended regimen with mifepristone and misoprostol."

3. Line 229: Please further explain why you suggest prescribing opioids in some circumstances when you have clearly shown that oxycodone does not reduce the amount or duration of maximum pain experienced or the duration of overall pain in women undergoing medical abortion.

We realize in retrospect that this sounds contradictory. We have tried to clarify our recommendations (see response to reviewer 1, item 3).

Reviewer #3: This is a randomized controlled trial comparing oxycodone 10 mg versus placebo taken at the onset of cramping on maximum pain within 24 hours post-misoprostol in women

undergoing first trimester medical abortion. The authors found no difference in max pain between the two treatment groups. Overall, this study is well-done and relevant to those who provide medical abortions to understand how much narcotics are being used and to adjust their prescribing patterns.

Abstract:

1. Line 30: When was the text message sent within the 24 hour period after misoprostol?

We launched the text messages when subjects notified us of misoprostol intake (time 0). We have included the timing of the launch and the following text messages in lines 126-128 “Study staff launched the text message platform when subjects notified them of misoprostol ingestion (0 hours). At 6 and 24 hours, subjects responded to an automated survey via text (TextIt, Trileet Inc., USA)”

2. Line 33: Satisfaction with what? Pain control?

This was clarified in line 64: “reported satisfaction with pain medications”

3. Lines 38-9: For the mean duration of maximum pain, the SD is larger than the mean given, which suggests that the distribution is not normal. I recommend re-analyzing using the median duration of maximum pain instead.

We have changed duration of maximum pain to median in the Tables 2 and 3, as well as in the body of the manuscript.

4. Line 44: "or other outcomes" is vague. I would specify what the outcomes are.

We agree and have removed this ‘or other outcomes’. We have not added the additional outcomes in order to stay within the designated abstract word count.

Introduction

1. The introduction is succinct and provides sufficient background to highlight the compelling reasons to perform this study. Consider adding in references for variations in physician prescribing patterns (Guilbert ER Can Fam Physician 2016; Fiala C Eur J Obstet Gynecol Reprod Biol 2018).

Thank you for the suggestion. These citations were added to lines 82-84 to further demonstrate the variation in physician prescribing patterns.

Methods

1. The primary outcome and secondary outcomes are not clearly stated in the methods section.

We have added a paragraph (paragraph 3, lines 113-118) to the methods section in order to clearly state this information.

2. Lines 117-8: The authors state that to allow for 10% drop-out, they planned to enroll 38 participants per group for a total of 152 participants. It appears that the authors are also stratifying by gestational age, can the authors clarify this in the text?

Correct, we did also stratify by gestational age group. We have reworked lines 143-155 to clarify this issue. It now reads: “We based our sample on the assumptions of non-normally-distributed data, and used a Wilcoxon rank-sum test data simulation using specified parameters (delta=2, sigma=2.6, alpha=.05) for a moderate effect. A sample size of 34 participants per group provided

80% probability of detecting the 2-point difference in the simulated data. To allow equal power for stratification by the two gestational age groups, we doubled the sample and to allow for up to 10% drop-out, we planned to enroll 152 participants (<7wks: 38 placebo, 38 oxycodone; 7-10wks: 38 placebo, 38 oxycodone). Prior to completion of the study, without breaking the randomization schema or further evaluating outcomes, we found that 30.8% of enrolled subjects had not taken study drug. Therefore, we increased the total enrollment by 25% in the <7 week group to a total of 176 participants in order to have sufficient power to determine our primary outcome (<7wks: 48 placebo, 48 oxycodone; 7-10wks: 38 placebo, 38 oxycodone)."

3. Which statistical analysis tests did the authors use? It is not included in the text or in the tables.

We have further clarified our statistical methods in Lines 165-170: "We used independent two-sample t-tests to compare continuous variables, chi-square tests to compare categorical variables and Wilcoxon rank-sum tests to compare medians. Odds ratios were computed using simple logistic regression. We analyzed primary our primary cohort using an intent-to-treat approach. Additionally, we performed a per protocol analysis."

Results

1. Did anyone require more than the 6 adjunctive oxycodone tablets? How were the participants instructed to use the oxycodone (e.g. 1 tab every 2 hours?)

No subject reported using more than the 6 adjunctive oxycodone tablets. Every patient received a paper prescription for 6 tablets of oxycodone and they were instructed that they could chose to fill the prescription at the pharmacy of their choice or not and use it at their own discretion. We have added information into lines 123-125 that reads: "we provided subjects a paper prescription for six oxycodone 5mg oral tablets (1 tablet orally every 4 hours as needed for pain) to fill and use only if needed ('adjunctive' medication). Line 198-199 was added to the results section "No one reported using more than the 6 tablets prescribed."

2. Lines 178 on: Typically the outcome of "successful medical abortion" is defined as passage of pregnancy without need for surgical intervention. Therefore, those participants who completed with another dose of misoprostol and with expectant management wouldn't be counted as a "unsuccessful". Since the secondary outcomes are not specified in the methods, it's unclear what the authors are trying to show with these results (safety of med abortion? Pain difference for the 3 ongoing vs not?) The numbers are so small in this group that it doesn't seem relevant to do many comparisons with the "successful" group.

We have reworked this section in order to ensure clarity around these definitions. This paragraph has been revised to follow these definitions. We agree that due to the small numbers in this group, it is not necessary to report in the final manuscript and has been removed.

Lines 227-232: "Two women had incomplete abortions or an ongoing pregnancy requiring surgical aspiration (oxycodone 1, placebo 1) as confirmed at their follow-up appointment which is consistent with the typical completion rate for medical abortion of 95-99%.² One additional women required an extra dose of misoprostol to complete, whereas one participant completed with expectant management (oxycodone 2, placebo 0). All of these subjects reported by text survey that they believed they had passed the pregnancy."

3. Overall, the results section is 2.5 pages long. Much of the info presented in the text is also in the tables. Can the authors streamline the results section to avoid reader fatigue?

Thank you for the feedback. The results section was edited and shortened. We have removed many of the secondary analyses that had small numbers with non-significant findings.

Discussion

1. Do the authors have enough info from the placebo group to describe what the usual pain course is for patients undergoing medical abortion?

We do but actually the usual pain course was no different between the groups. We have added some information about this in the discussion section. Lines 246-249: "Our study also helps to further characterize the pain experienced by women undergoing medical abortion as it has not been well-described. Women reported a relatively high peak pain level of 8 out of 10 on a NRS miwhich occurred 2 ½ to 4 hours after misoprostol use and lasted for about 1 hour."

Figures/Tables

1. Figure 1- For the screen fail (n=10), can the authors describe what the "other" is since there is only 1 participant in this group? The numbers don't add up for "allocated to placebo" under gestational age <7 weeks and "allocated to oxycodone" under gestational age 7-10 weeks. How many people completed the 6 hour text message and the 24 hour text message? When was the primary outcome determined?

Upon review of our enrollment logs, we were able to clarify that the "other" patient was not enrolled due to marijuana use >4x per week. This has been updated in the consort diagram (Figure 1). There was one participant in each group that was lost to follow-up that did not respond to any text message data. This is accounted for in the lost to follow-up box below the allocated groups in Figure 1. Otherwise, 170/172 participants completed all portions of the text message surveys. We have clarified this in line 174-175: "Text message surveys were completed by 170/172 (98.8%) of participants." The primary outcome was maximum reported pain 24 hours post-misoprostol. This is described in lines 113-118: "Our primary outcome was to determine if women who receive oxycodone 10mg and ibuprofen 800mg undergoing medical abortion will report maximum pain scores at least 2 points lower on a NRS compared to women using ibuprofen 800mg and placebo within 24 hours post-misoprostol."

STATISTICAL EDITOR COMMENTS:

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

lines 30-31, 36-39, 110-120: Need to separate the (1) primary outcome from all the others (including subset by GA), those are secondary outcomes, were not factored into the power/sample size calculation. None of the secondary outcomes that were NS can be generalized, since they were not primary.

We agree that this was not clear in the original manuscript. We had sufficient power for each gestational age strata. We have clarified the power calculation by revising lines 143-155: "We based our sample on the assumptions of non-normally-distributed data, and used a Wilcoxon rank-sum test data simulation using specified parameters (delta=2, sigma=2.6, alpha=.05) for a moderate effect. A sample size of 34 participants per group provided 80% probability of

detecting the 2-point difference in the simulated data. To allow equal power for stratification by the two gestational age groups, we doubled the sample and to allow for up to 10% drop-out, we planned to enroll 152 participants (<7wks: 38 placebo, 38 oxycodone; 7-10wks: 38 placebo, 38 oxycodone). Prior to completion of the study, without breaking the randomization schema or further evaluating outcomes, we found that 30.8% of enrolled subjects had not taken study drug. Therefore, we increased the total enrollment by 25% in the <7 week group to a total of 176 participants in order to have sufficient power to determine our primary outcome (<7wks: 48 placebo, 48 oxycodone; 7-10wks: 38 placebo, 38 oxycodone)."

Table 1: If any participant characteristics had been statistically different, then that is thought to be due to random chance, since the cohorts were randomly chosen. No need to include column of stats.

Table 1: The column of p-values was removed.

Table 2 and Fig 1: Per the flow diagram, there were 2 patients lost to follow-up before the 6h and 24h measures of pain score. Therefore, how can there be 86 +86 patients available for the primary outcome (and others) as cited in Table 2? Also, the primary outcome was max pain score, not duration of pain score or proportion having pain scores > 7, etc. Need to clearly separate the primary outcome from all the others, they were secondary.

Table 2 was edited to reflect the 85 women in each cohort that were analyzed. Additionally primary and secondary outcomes were separated using the insertion of a header.

Table 3: This analysis by subset was not factored into the primary power/sample size analysis, has lower counts than the aggregate and should not be labelled as a primary outcome. If it had been, then the initial inference threshold would have to have been $p < .017$, rather than the $p < .05$ inference threshold for 1 primary outcome. Since these comparisons were under powered, none of the NS findings can be generalized.

Thank you for this comment. We are overpowered for the combined group and powered for stratification by gestational age, therefore no change was made to our analysis.

Fig 1: What were the baseline characteristics of the 75+5=80 women who either declined or were not included due to staff unavailable? That is, was the final randomized cohort representative of all the women who would have been eligible?

We did not collect baseline characteristics on subjects who were not randomized. Line 108-109 was added to state this: "We did not collect baseline demographics on subjects who were not randomized."

Fig 1 and Supplemental material: Since there were 49 women (~ 28%) who did not take the allocated intervention, the per protocol analysis should be included in the main text, not in supplemental, (at least that portion related to the primary outcome.)

Appendix 4 from the supplemental materials was placed in the main body of the text as Table 4. The results are referenced in lines 208-211: "We found no differences in baseline characteristics, maximum reported pain score, duration of pain, number of ibuprofen tablets used, proportion of participants who filled and used oxycodone, or satisfaction (Table 4)."

Also in supplemental: Rather than (app 3), comparing the participant characteristics of Oxy vs placebo in the PP analysis, should compare the PP subsets vs those who were randomized, but then were allocated to a different treatment, in order to determine whether those who were allocated to the different treatment differed in ways that might affect the analysis of the max pain scores. Appendix 6 table was created to address this and can now be found in the supplementary section. We did not see any differences between baseline characteristics of protocol followers vs non-protocol followers. The results comparing protocol followers vs non-protocol followers is demonstrated in appendix 7.

EDITOR COMMENTS:

1. Thank you for your submission to Obstetrics & Gynecology. Your paper is very well written. Please pay particular attention to the Statistical Editor's points as these must be addressed clearly. 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.

- 18 years

This was added to line 98.

- We prefer to avoid providing p values only unless that is the only appropriate test of significance. Where possible in the abstract AND the text, please provide an effect size (such as an OR or RR) and 95% CI's.

Where appropriate, effect size and 95% confidence intervals were replaced in the manuscript.

- how about "by 99.4%"?

Line 174-175 was edited to "Text message surveys were completed by 170/172 (98.8%) of participants."

- We do not allow authors to describe variables or outcomes in terms that imply a difference (such as the terms "trend" or "tendency" or "marginally different") unless there is a statistical difference. Please edit here and throughout.

We have changed this in lines 217-218 to: "Blinding to allocation group was adequate (placebo 70%, oxycodone 47% p=.09)."

- Is this rate typical for medical abortion?

Yes, the rates of successful medical abortion were similar in our study to the known expected outcomes. We have added some information about this in Lines 227-229 changed to clarify: "Two women had incomplete abortions or an ongoing pregnancy requiring surgical aspiration (oxycodone 1, placebo 1) as confirmed at their follow-up appointment which is consistent with the typical completion rate for medical abortion of 95-99%.²"

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. 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.

[All disclosures were added to the title page.](#)

4. Clinical trials submitted to the journal as of July 1, 2018, must include a data sharing statement. The statement should indicate 1) whether individual deidentified participant data (including data dictionaries) will be shared; 2) what data in particular will be shared; 3) whether additional, related documents will be available (eg, study protocol, statistical analysis plan, etc.); 4) when the data will become available and for how long; and 5) by what access criteria data will be shared (including with whom, for what types of analyses, and by what mechanism).

Responses to the five bullet points should be provided in a box at the end of the article (after the References section).

[The following statement was added below the References section:](#)

[The authors are willing to share their de-identified data and materials with other eligible investigators through academically establish means. OHSU maintains a high community standard for the free release of data and materials. Transfer of resources is subject to the acceptance of a Materials Transfer Agreement as required by policy at OHSU. OHSU understands and agrees to comply with the NIH policy on Sharing Research Data and on Sharing Model Organisms.](#)

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.

[All definitions in the manuscript are consistent with the revitalize definitions.](#)

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.

[The manuscript meets the length restrictions as set by the Green Journal.](#)

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- * 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.

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

[We have complied. Our running foot is "Opioid Analgesia for Medical Abortion"](#)

9. 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."

[Our Précis reads in lines 38-39: "Précis: Oxycodone does not reduce the maximum level of pain experienced by women undergoing medical abortion up to 10 0/7 weeks gestation."](#)

10. 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.

The abstract has been reviewed and mirrors the results in the body of the paper. The word count for the abstract is 298.

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http://edmgr.ovid.com/ong/accounts/sampleabstract_RCT.pdf. Please edit your abstract as needed.

The abstract is structured according to the journal's standard format.

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Standard abbreviations and acronyms have been reviewed.

13. 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.

Use of the virgule symbol to express data was utilized in lines 130-133.

14. 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.

Thank you for the feedback. Where appropriate, OR and RR with 95% CI were replaced to make the results more clinically relevant.

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%).

All percentages and p-values are within guidelines.

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The tables in the journal conform to standard guidelines.

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17. Figure 1: Please confirm or explain n values for those allocated to placebo for <7 weeks (34+13=47) and those allocated to oxycodone for 7-10 weeks (24+13=37).

Lines 143-155 further clarify:

“We based our sample on the assumptions of non-normally-distributed data, and used a Wilcoxon rank-sum test data simulation using specified parameters (delta=2, sigma=2.6, alpha=.05) for a moderate effect. A sample size of 34 participants per group provided 80% probability of detecting the 2-point difference in the simulated data. To allow equal power for stratification by the two gestational age groups, we doubled the sample and to allow for up to 10% drop-out, we planned to enroll 152 participants (<7wks: 38 placebo, 38 oxycodone; 7-10wks: 38 placebo, 38 oxycodone). Prior to completion of the study, without breaking the randomization schema or further evaluating outcomes, we found that 30.8% of enrolled subjects had not taken study drug. Therefore, we increased the total enrollment by 25% in the <7 week group to a total of 176 participants in order to have sufficient power to determine our primary outcome (<7wks: 48 placebo, 48 oxycodone; 7-10wks: 38 placebo, 38 oxycodone).”

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