

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: Jan 14, 2022
To: "Alisa B. Goldberg" [REDACTED]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-21-2423

RE: Manuscript Number ONG-21-2423

Mifepristone and misoprostol for undesired pregnancy of unknown location

Dear Dr. Goldberg:

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).

Please be sure to address the Editor comments (see "EDITOR COMMENTS" below) in your point-by-point response.

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 Feb 04, 2022, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: This is a retrospective cohort study comparing the outcomes of immediately starting medication abortion in the setting of pregnancy of unknown location compared to waiting to locate the pregnancy prior to initiating medication abortion. The study provides valuable clinical information to counsel patients and inform clinical practice.

Clarifications below:

1. Methods: The selection of patients is a bit confusing, initially they were selected based on an LMP
2. Methods: Why was the number of patients offered same day start so low? Did this change over time? What influenced the providers to offer same day vs. delayed start? Ectopic symptoms?
3. Methods: line 211 Table 5, were the 9 adverse events in 9 individual patients or were they overlapping?
4. Figure 1: Can you continue the flow chart and report on numbers in each group lost to follow up?
5. Discussion: Line 282-284 is an important point that should be discussed with patients.

Reviewer #2: This is a well written, excellent and timely paper that challenges the way that abortion services are performed. It gives provides safety data and gives support to the option of providing medication abortion without definitive diagnosis of intrauterine pregnancy. Kudos. Please see below for a few suggestions for improvement.

Precis: See comments for results and diagnosis. Without additional information, the conclusion that the immediate abortion initiation excludes abortion more rapidly is unsupported.

Abstract: As below, the conclusion that ectopic pregnancy is excluded more rapidly in the immediate start group may be more of a function of study design than method/process superiority.

Introduction

1. Line 63 - 65: "...uterine emptying with medications may also facilitate diagnosis of pregnancy location more rapidly..." Given that follow-up of a PUL for possible ectopic pregnancy often occurs as frequently as every 2 days, this may be a bit of a stretch. Is there a citation for this? If not, consider adding a bit more explanation.

2. Line 69: Consider replacing "determining diagnosis" to "confirming intrauterine pregnancy"

Methods

1. Please clarify if there was a standard protocol for following the "delay for diagnosis" patients? If not, please describe the most common practices for follow-up. Knowing how this group was followed is extremely important as we compare the two groups

2. Line 116 - 117: "Non-adherence with follow-up was defined as 30 days without clinical contact..." Why was 30 days selected as the definition? In the context of PUL/evaluation of ectopic, 30 days is a long time, especially when considering the catastrophic outcomes that could occur. Was a shorter timeframe considered, such as 7 to 14 days?

3. Line 117 - 120: "Significant adverse events included... occurring within 3 month of initial presentation." Similarly, why was 3 months selected as the definition in this study? Given the known safety profile of mifepristone/misoprostol and natural history of ectopic pregnancy, any related adverse event would occur well before 90 days.

4. Please indicated if race/ethnicity was self-identified. Additionally, when selecting a race/ethnic group, was more than one selection possible?

5. With respect to your sample size calculations, please specify how many subjects were required in each group to maintain adequate power (in addition to the overall sample size)

Results

1. Line 202 - 203: Consider adding additional information to the sentence "Overall, a total of 233 (52.0%) patients in the delay-for-diagnosis group never took mifepristone" such as "due to spontaneous early pregnancy loss, ectopic pregnancy, or unknown reasons." There are a lot of associated tables and figures. Just a bit of additional information will prevent the reader from having to go to another table.

2. Having minimal information about how the "delay for diagnosis" group was managed makes comparing the groups with respect to time to diagnosis and time to complete abortion. For example, does the difference in time to diagnosis between the groups truly reflect superiority of the "same day start" group or is it more of a reflection of provider discretion (e.g., repeating an US in 1 week vs. 2 days where there is little suspicion for ectopic pregnancy). Similarly, did the clinician choose to follow the delay group at 1 week instead of 3-5 days as in the immediate group? As above, please provide additional information as to how the "delay for diagnosis" group was managed.

Discussion

1. As above, the "same day start" group may have had a shorter time to rule out ectopic pregnancy and shorter time to completed abortion by design. Thus, while there is certainly benefit, without additional information, the conclusion that same day start provides a diagnostic benefit is unsupported.

2. Line 282 - 284: Consider revising the sentence to read something such as "In the US, patients may have health insurance..." Removing the word "many" makes the sentence consistent with the fact that many patients are uninsured and underinsured as well as the fact that many commercial insurance plans cover abortion services (and law/policy may prevent the patient from using the coverage)

. Line 292 - 293: As above, the conclusion that there is diagnostic benefit is unsupported without additional information.

Table 1

1. Please revise to clarify the overall protocol. For example, what day is misoprostol given. Is day 3 - 5 after the misoprostol day 4 -6 of the overall protocol? What is a formal ultrasound? A radiology US? MFM US?

Table 4: This information could be integrated into the text, eliminating the need for this table

Figure 1: Consider adding another arrow and block below "same day start" to indicate that 17 patients were removed/not analyzed (n=38) as they did not meet protocol criteria

Reviewer #3: Thank you for the opportunity to review this manuscript. This historical cohort study illuminates several important considerations in the management of PULs. The finding that immediate initiation does not lead to increased risks is significant along with the finding of lower medication abortion efficacy. Both of these improve providers' ability to inform patients and participate in improved shared-decision making about how to best approach and unwanted pregnancies classified as a PUL. I have the following suggestions and comments:

Major:

1. My main concern has to do with the finding that no ectopic pregnancies were identified in the same day start group. Your discussion provides good reasoning as to why this may have happened. However, your power sample calculation is

confusing since you have unequal groups. You say you need 200 subjects which it appears to be in each group so then say you wanted 500 patients. However, even though you had 452 patients you had unequal groups so you oversampled in the delay group and under in the same day start. Consider a new power calculation that accounts for unequal groups or at the very least provide a post ad hoc power calculation using your results.

2. Do you have information on hcgs? would be helpful to see that data. Was there a beta level in the delay group that was more commonly associated with ectopics? i assume not but would be interesting to see the data or explain why it was not included. Also helpful to know for same day starts if you did anything different with a high quant, e.g. >2000. You show this in Table 1 but don't really provide any information about this. Were most of the ER visits in same day because of need for formal scan?

3. Results lines 187-190- you say you excluded those with major risk factors but then say that they were more common amongst those that ended up with ectopics. Please clarify. I also think you could consider including the ones with risk factors since it doesn't always mean that they have an ectopic.

Minor comments

1. Precis- I am not sure if you can say that same day start excludes ectopic pregnancy- that seems to imply that it treated it which we can't say for certain.

2. Intro- would help to say incidence of ectopics, and esp under 42 days. Also helpful to remind readers of need for immediate identification of ectopics given high risk or morbidity and mortality.

3. Line 55- I would remove persistent PUL since that is not a diagnosis but rather an ongoing classification.

4. Intro- would help to bring up that current mifepristone labeling includes ectopic pregnancy as a contraindication, may also want to include off-label use in your discussion.

5. Line 65- i believe there is evidence out there about many patients wanting medical aspiration and would also cite the increasing popularity (see Guttmacher).

6. Line 67 you discuss same day start based on varying recommendation. I am familiar with PP MS&Gs but that recommendation is up to 35 days from sure LMP. Would be helpful to specify GA range of the recommendation and then in methods explain why you chose 42.

7. Discussion lines 271-8 would also include a point as to how your data improved ability to make shared decisions. Some patients may prefer to wait even with lower efficacy while others are willing to take risk of lower efficacy with change it will get the result faster.

8. Discussion regarding how medication abortion may impact tubal abortions- my teaching was that the fallopian tube does not have progesterin receptors so would not be effective. Can you comment on this?

STATISTICAL EDITOR COMMENTS:

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

Table 2: As can be seen from this Table, although "Ectopic symptom:Any", "Vaginal bleeding" or "Major risk factor:Any" are each statistically associated with occurrence of EP, there would be high rates of false positives and low rates of PPV were those to be applied in individual cases.

Table 3: The groups were not randomized and differed significantly in GA by LMP, proportion with uncertain LMP and any ectopic symptoms, so the crude rates of EP outcomes may not be a valid comparison.

Table 5: The study is underpowered to discern a difference in serious adverse events due to low counts of adverse events. The study is also underpowered to discern differences in ER visits or non-adherence to follow-up. For the former, the rate among the ER visits for same day start would have to exceed 53% or be < 14% in order to fulfill the usual 80% power and $\alpha = 0.05$, given the sample sizes at hand. Similarly, for non-adherence with follow-up, the same day cohort would have to exceed 33.4% or be < 2.6%, assuming the same power/sample size inputs and a baseline rate = 15.9%. For the safety outcomes, should not the power limitation and include CIs with the point estimates in Table 5.

Figs 2, 3: Need to include at time points on the x-axes, the "N" remaining in each cohort. Should include 0,5,10,15, 20 and 25 days at minimum.

EDITOR COMMENTS:

General: Please rephrase the statements in your submission to avoid using causal language.

1. The Editors of Obstetrics & Gynecology have increased transparency around its peer-review process, in line with efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online. Additionally, unless you choose to opt out, we will also be including your point-by-point response to the revision letter. If you opt out of including your response, only the revision letter will be posted. Please reply to this letter with one of two responses:

- A. OPT-IN: Yes, please publish my point-by-point response letter.
- B. OPT-OUT: No, please do not publish my point-by-point response letter.

2. When you submit your revised manuscript, please make the following edits to ensure your submission contains the required information that was previously omitted for the initial double-blind peer review:

- * Include your title page information in the main manuscript file. The title page should appear as the first page of the document. Add any previously omitted Acknowledgements (ie, meeting presentations, preprint DOIs, assistance from non-byline authors).
- * Funding information (ie, grant numbers or industry support statements) should be disclosed on the title page and in the body text. For industry-sponsored studies, the Role of the Funding Source section should be included in the body text of the manuscript.
- * Include clinical trial registration numbers, PROSPERO registration numbers, or URLs at the end of the abstract (if applicable).
- * Name the IRB or Ethics Committee institution in the Methods section (if applicable).
- * Add any information about the specific location of the study (ie, city, state, or country), if necessary for context.

3. Obstetrics & Gynecology uses an "electronic Copyright Transfer Agreement" (eCTA), which must be completed by all authors. When you uploaded your manuscript, each co-author received an email with the subject, "Please verify your authorship for a submission to Obstetrics & Gynecology." Please check with your coauthors to confirm that they received and completed this form, and that the disclosures listed in their eCTA are included on the manuscript's title page.

4. For studies that report on the topic of race or include it as a variable, authors must provide an explanation in the manuscript of who classified individuals' race, ethnicity, or both, the classifications used, and whether the options were defined by the investigator or the participant. In addition, the reasons that race/ethnicity were assessed in the study also should be described (eg, in the Methods section and/or in table footnotes). Race/ethnicity must have been collected in a formal or validated way. If it was not, it should be omitted. Authors must enumerate all missing data regarding race and ethnicity as in some cases, missing data may comprise a high enough proportion that it compromises statistical precision and bias of analyses by race.

Use "Black" and "White" (capitalized) when used to refer to racial categories. The nonspecific category of "Other" is a convenience grouping/label that should be avoided, unless it was a prespecified formal category in a database or research instrument. If you use "Other" in your study, please add detail to the manuscript to describe which patients were included in that category.

5. Your submission indicates that one or more of the authors is employed by a pharmaceutical company, device company, or other commercial entity. This must be included as a statement in the Financial Disclosure section on the title page.

6. 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 Methods section of the body text, 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 website outlining the exempt data sets or a letter from a representative of the IRB. In addition, insert a sentence in the 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.

7. Please submit a complete STROBE checklist with your revision.

Responsible reporting of research studies, which includes a complete, transparent, accurate and timely account of what was done and what was found during a research study, is an integral part of good research and publication practice and not an optional extra. Obstetrics & Gynecology supports initiatives aimed at improving the reporting of health research, and we ask authors to follow specific guidelines for reporting randomized controlled trials (ie, CONSORT), observational studies (ie, STROBE), observational studies using ICD-10 data (ie, RECORD), meta-analyses and systematic reviews of randomized controlled trials (ie, PRISMA), harms in systematic reviews (ie, PRISMA for harms), studies of diagnostic accuracy (ie, STARD), meta-analyses and systematic reviews of observational studies (ie, MOOSE), economic evaluations

of health interventions (ie, CHEERS), quality improvement in health care studies (ie, SQUIRE 2.0), and studies reporting results of Internet e-surveys (CHERRIES). Include the appropriate checklist for your manuscript type upon submission. Please write or insert the page numbers where each item appears in the margin of the checklist. Further information and links to the checklists are available at <http://ong.editorialmanager.com>. In your cover letter, be sure to indicate that you have followed the CONSORT, MOOSE, PRISMA, PRISMA for harms, STARD, STROBE, RECORD, CHEERS, SQUIRE 2.0, or CHERRIES guidelines, as appropriate.

8. 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 5,500 words. Stated word limits include the title page, précis, abstract, text, tables, boxes, and figure legends, but exclude references.

9. 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).
- * If your manuscript was uploaded to a preprint server prior to submitting your manuscript to Obstetrics & Gynecology, add the following statement to your title page: "Before submission to Obstetrics & Gynecology, this article was posted to a preprint server at: [URL]."

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 limit for Original Research articles is 300 words; Reviews is 300 words; Case Reports is 125 words; Current Commentary articles is 250 words; Executive Summaries, Consensus Statements, and Guidelines are 250 words; Clinical Practice and Quality is 300 words; Procedures and Instruments is 200 words. Please provide a word count.

11. ACOG avoids using "provider." Please replace "provider" throughout your paper with either a specific term that defines the group to which are referring (for example, "physicians," "nurses," etc.), or use "health care professional" if a specific term is not applicable.

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.

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.

14. Please review examples of our current reference style at <http://ong.editorialmanager.com> (click on the Home button in the Menu bar and then "Reference Formatting Instructions" document under "Files and Resources"). Include the digital object identifier (DOI) with any journal article references and an accessed date with website references. Unpublished data, in-press items, personal communications, letters to the editor, theses, package inserts, submissions, meeting presentations, and abstracts may be included in the text but not in the reference list.

In addition, 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 references you are citing are still current and available. Check the Clinical Guidance page at <https://www.acog.org/clinical> (click on "Clinical Guidance" at the top). If the reference is still available on the site and isn't listed as "Withdrawn," it's still a current document.

If the reference you are citing has been updated and 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.

15. Figures 1-3 may be resubmitted as-is with the revision.

16. 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 <https://wkauthorservices.editage.com/open-access/hybrid.html>.

If your article is accepted, you will receive an email from the editorial office asking you to choose a publication route (traditional or open access). Please keep an eye out for that future email and be sure to respond to it promptly.

If you choose open access, you will receive an Open Access Publication Charge letter from the Journal's Publisher, Wolters Kluwer, and instructions on how to submit any open access charges. The email will be from publicationservices@copyright.com with the subject line, "Please Submit Your Open Access Article Publication Charge(s)." Please complete payment of the Open Access charges within 48 hours of receipt.

If you choose to revise your manuscript, please submit your revision through Editorial Manager at <http://ong.editorialmanager.com>. Your manuscript should be uploaded as a Microsoft Word document. 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. Do not omit your responses to the Editorial Office or Editors' comments.

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 Feb 04, 2022, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Jason D. Wright, MD
Editor-in-Chief

2020 IMPACT FACTOR: 7.661
2020 IMPACT FACTOR RANKING: 3rd 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.

February 1, 2022

Dear Editors of Obstetrics & Gynecology,

Thank you for the opportunity to submit revisions to our manuscript: *"Mifepristone and misoprostol for undesired pregnancy of unknown location"*.

We have read the Instructions for Authors and attach below a point-by-point response to each of the comments in the review letter.

We will separately attach the revised unblinded manuscript, as well as a revised STROBE checklist



Sincerely,

A handwritten signature in black ink, appearing to be 'Alisa B. Goldberg'.

Alisa B. Goldberg, MD, MPH
Associate Professor of Obstetrics, Gynecology and Reproductive Biology
Harvard Medical School
Director, Division of Family Planning and Complex Family Planning Fellowship
Brigham and Women's Hospital
Vice President, Research and Clinical Training
Planned Parenthood League of Massachusetts

REVIEW OBSTET GYNECOL

RE: Manuscript Number ONG-21-2423

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Clarifications below:

1. Methods: The selection of patients is a bit confusing, initially they were selected based on an LMP ≤ 42 days in the EMR, however, according to Table 3, many patients had an unknown LMP. Please clarify this. [Table 3 lists patients with 'uncertain LMP', not 'unknown LMP. When patients call to make an appointment, they are asked about their LMP and scheduled accordingly. Phone schedulers are not clinicians and do not inquire about the certitude of menstrual dating. We included in our database, patients who reported an LMP of \$\leq 42\$ days on their initial phone scheduling appointment.](#)

Additionally, why not search the medical record for all patients with a PUL ultrasound diagnosis regardless of LMP reported at the time of the appointment? That may have increased the sample size. [Our study sought to compare "same-day-start", a new clinical management option, to the standard-of-care management option "delay for diagnosis". Since offering 'same-day-start' in the setting of PUL was a new clinical practice with an unproven safety profile, only patients believed to be at reasonably low risk for ectopic were eligible for same-day-start. Patients with a known LMP of more than 42 days and no evidence of an intrauterine gestational sac on transvaginal ultrasound would be considered higher risk for ectopic and therefore were not eligible for same-day start per PPLM protocols.](#)

[In order to minimize bias in this retrospective study, we sought to compare two different clinical management paradigms between groups that were otherwise as comparable as possible, thus, we only included those with known LMP \$\leq 42\$ days in both groups. Similarly, for all our comparative analyses, we excluded all subjects who had a prior ectopic, an IUD in situ at the time of conception and prior tubal surgery, because these patients would have been ineligible for same-day-start per PPLM protocols.](#)

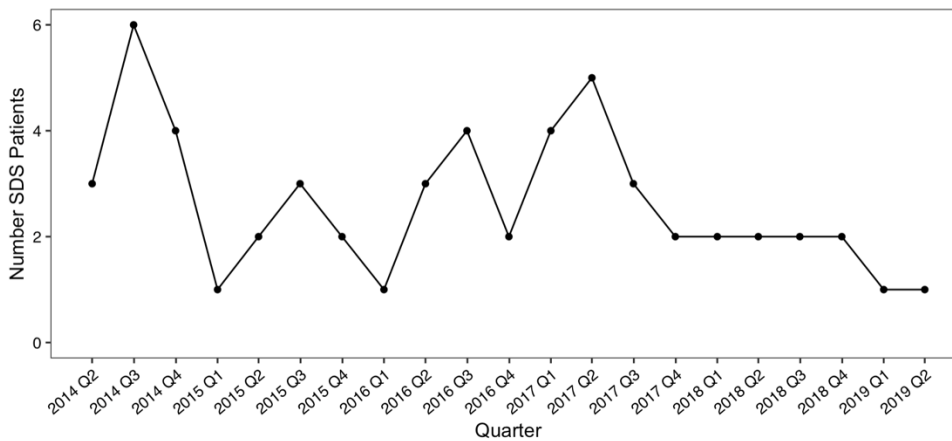
Table 1 does not list known LMP as a requirement for initiating medication abortion while simultaneously determining pregnancy location.

[Table 1 describes management of same-day-start patients. Eligibility criteria for same-day-start is reported in lines 106-108 in the text and states that patients were required to have a known LMP of \$\leq 42\$ days.](#)

2. Methods: Why was the number of patients offered same day start so low? Did this change over time? What influenced the providers to offer same day vs. delayed start? Ectopic symptoms?

[Table 3 demonstrates that providers were less likely to offer same-day-start to patients with an uncertain LMP and any ectopic symptoms. They were also more likely to offer same-day-start to those earlier in gestation by LMP, when an empty uterus on ultrasound is more likely to be a normal finding. We did not identify any other differences in sociodemographics or reproductive history between groups. We similarly did not note an obvious trend in the frequency with which same-day start was offered over time, except perhaps rate stabilization in 2018 \(see chart below\).](#)

[It is not clear why the number of participants offered same-day-start was so low, and whether this was due to a scarcity of patients with a sure, early LMP and no concerning bleeding or pain OR due to general clinician discomfort offering a new management option prior to the publication of outcome/safety data.](#)



3. Methods: line 211 Table 5, were the 9 adverse events in 9 individual patients or were they overlapping? [9 individual patients had a major adverse event \(several individuals had more than one adverse event\). We have clarified this in Table 5.](#)

4. Figure 1: Can you continue the flow chart and report on numbers in each group lost to follow up? [Done.](#)

5. Discussion: Line 282-284 is an important point that should be discussed with patients. [Thank you](#)

Reviewer #2: This is a well written, excellent and timely paper that challenges the way that abortion services are performed. It gives provides safety data and gives support to the option of providing medication abortion without definitive diagnosis of intrauterine pregnancy. Kudos. Please see below for a few suggestions for improvement. [Thank you!](#)

Precis: See comments for results and diagnosis. Without additional information, the conclusion that the immediate abortion initiation excludes abortion more rapidly is unsupported.

Abstract: As below, the conclusion that ectopic pregnancy is excluded more rapidly in the immediate start group may be more of a function of study design than method/process superiority.

Introduction

1. Line 63 - 65: "...uterine emptying with medications may also facilitate diagnosis of pregnancy location more rapidly..." Given that follow-up of a PUL for possible ectopic pregnancy often occurs as frequently as every 2 days, this may be a bit of a stretch. Is there a citation for this? If not, consider adding a bit more explanation. [We have added the words "it is plausible that"...uterine emptying with medications may facilitate diagnosis of pregnancy location more rapidly...](#)

2. Line 69: Consider replacing "determining diagnosis" to "confirming intrauterine pregnancy" [Done.](#)

Methods

1. Please clarify if there was a standard protocol for following the "delay for diagnosis" patients? If not, please

describe the most common practices for follow-up. Knowing how this group was followed is extremely important as we compare the two groups

[We have added a description of the clinical management of the delay-for-diagnosis group to the methods section \(new lines 137-147\)](#)

2. Line 116 - 117: "Non-adherence with follow-up was defined as 30 days without clinical contact..." Why was 30 days selected as the definition? In the context of PUL/evaluation of ectopic, 30 days is a long time, especially when considering the catastrophic outcomes that could occur. Was a shorter timeframe considered, such as 7 to 14 days? [We concur that no clinical contact for >30 days with a PUL is a very long time, extremely troubling given the potential catastrophic outcomes that could occur and resource-intensive for clinical staff attempting to contact these patients. Since this study primarily aimed to compare the safety of same-day-start \(new option\) to delay-for-diagnosis \(standard of care\), we felt that if patients were 'non-adherent' with follow-up, that would unquestionably represent a significant safety concern.](#)

[We struggled with how to best measure and report on adherence and how to distinguish "adherence with follow-up" and "achieving a final definitive diagnosis". Ultimately, we chose to make "non-adherence", the extreme, a binary safety variable. Patients could still be coded as "adherent", if they complied with some follow-up, even if a definitive diagnosis was never achieved. Utilizing shorter 'gaps' in follow-up was challenging to operationalize as a safety measure. This has been clarified in the methods section and Table 4.](#)

3. Line 117 - 120: "Significant adverse events included... occurring within 3 month of initial presentation." Similarly, why was 3 months selected as the definition in this study? Given the known safety profile of mifepristone/misoprostol and natural history of ectopic pregnancy, any related adverse event would occur well before 90 days.

[We agree that most serious adverse events would be expected to occur well before 90 days, however we chose to scan the electronic health record for adverse events for 3 months from initial presentation to capture any delayed reporting of adverse outcomes. Patients with PUL are followed extremely closely by PPLM clinical staff, however, given our clinical volume and geographic reach, we sometimes learn of adverse events \(track down medical records\) at a date significantly later than when they occurred.](#)

[Additionally, we chose 3 months to roughly align with the first trimester, in particular to capture those who initially delayed-for-diagnosis and in some cases had their abortion at a much later date \(beyond the point of medication abortion eligibility\).](#)

4. Please indicated if race/ethnicity was self-identified. Additionally, when selecting a race/ethnic group, was more than one selection possible? [Race/ethnicity is self-reported in the PPLM EMR. Respondents can select Hispanic or non-Hispanic and one or more races. Individuals who select more than one race are lumped in with the "other" category. In our prior research, we discovered that 65% of all Hispanic individuals do not mark a race in our EMR, instead identifying Hispanic as their race \(Janiak et al Obstet Gynecol 2019\). For this reason, we report the combined race/ethnicity categories in our analyses.](#)

5. With respect to your sample size calculations, please specify how many subjects were required in each group to maintain adequate power (in addition to the overall sample size)

[Our initial sample size calculations were conducted before the data was pulled. For our primary continuous outcome of time to diagnose/exclude ectopic, we conducted sample size calculations assuming equal \(1:1\) and unequal \(2:1, 3:1\) split between groups. For all scenarios, we had >99% power to detect a difference of 5 days between delay for diagnosis and same day start with a sample size of 200 \(split unequally 150 for delay-for-diagnosis and 50 for same-day-start\). This aligned with our anticipated sample size, so we were powered for this primary analysis.](#)

[For all binary outcomes, our initial sample size calculations ensured that we had at least 80% power to detect differences of 15% between the two groups with a sample size of 200 \(even split between groups\). Given that the number of same-day-start patients was lower than the initial sample size calculations, we revisited our initial power calculations for our secondary binary safety outcomes where we did not find a significant difference. We had 80% power to detect the following differences: 9% in serious adverse events, 19% in emergency department visits, and 17% in non-adherence with follow-up. As these differences were close to our initial detectable differences, we still pursued these analyses.](#)

[We have added the following sentences to the Discussion section:](#)

[For patients with an undesired pregnancy who have a PUL on initial ultrasound, we found that initiating medication abortion with mifepristone on the day of presentation, with simultaneous close serial hCG follow-](#)

up (same-day-start) was associated with: 1) shorter time to rule out ectopic pregnancy; 2) shorter time to completed abortion; 3) a lower rate of successful medication abortion and higher rate of ongoing pregnancy when compared to delay-for-diagnosis. Additionally, in the same-day-start group, we found no evidence of an increase in the rates of serious adverse events, emergency department visits, or nonadherence with follow-up. However, we were underpowered to detect meaningful differences for these safety outcomes.

Results

1. Line 202 - 203: Consider adding additional information to the sentence "Overall, a total of 233 (52.0%) patients in the delay-for-diagnosis group never took mifepristone" such as "due to spontaneous early pregnancy loss, ectopic pregnancy, or unknown reasons." There are a lot of associated tables and figures. Just a bit of additional information will prevent the reader from having to go to another table.

[Done](#)

2. Having minimal information about how the "delay for diagnosis" group was managed makes comparing the groups with respect to time to diagnosis and time to complete abortion. For example, does the difference in time to diagnosis between the groups truly reflect superiority of the "same day start" group or is it more of a reflection of provider discretion (e.g., repeating an US in 1 week vs. 2 days where there is little suspicion for ectopic pregnancy). Similarly, did the clinician choose to follow the delay group at 1 week instead of 3-5 days as in the immediate group? As above, please provide additional information as to how the "delay for diagnosis" group was managed.

[We have added a description of how the delay-for-diagnosis group was managed in the methods section \(lines 137-147\).](#)

Discussion

1. As above, the "same day start" group may have had a shorter time to rule out ectopic pregnancy and shorter time to completed abortion by design. Thus, while there is certainly benefit, without additional information, the conclusion that same day start provides a diagnostic benefit is unsupported.

[Given that patients in both the same-day-start and delay-for-diagnosis groups are followed closely with serial hCG testing to exclude ectopic pregnancy and managed according to their hCG levels and trends \(see methods lines 137-147\), we believe our findings and conclusions hold. We have softened our conclusions given our retrospective design and in accordance with another reviewer's recommendation, present our findings as associations rather than causal.](#)

2. Line 282 - 284: Consider revising the sentence to read something such as "In the US, patients may have health insurance..." Removing the word "many" makes the sentence consistent with the fact that many patients are uninsured and underinsured as well as the fact that many commercial insurance plans cover abortion services (and law/policy may prevent the patient from using the coverage)

[Done](#)

. Line 292 - 293: As above, the conclusion that there is diagnostic benefit is unsupported without additional information.

[Additional information provided in the methods section.](#)

Table 1

1. Please revise to clarify the overall protocol. For example, what day is misoprostol given. Is day 3 - 5 after the misoprostol day 4 -6 of the overall protocol? What is a formal ultrasound? A radiology US? MFM US?

[The protocol has been clarified in Table 1. We have removed the word 'formal' and replaced it with 'diagnostic' ultrasound. At PPLM we refer patients out of the affiliate for diagnostic ultrasounds to academic medical centers or local private ultrasound practices. We expect the physicians interpreting ultrasounds at these sites are either radiologists or MFM specialists, however we do not know for certain.](#)

Table 4: This information could be integrated into the text, eliminating the need for this table

[The data in Table 4 has been incorporated into the flow diagram presented in Figure 1 and the table has been removed.](#)

Figure 1: Consider adding another arrow and block below "same day start" to indicate that 17 patients were removed/not analyzed (n=38) as they did not meet protocol criteria

[We did not remove these individuals from the overall flow diagram because in addition to our primary outcomes comparing same-day start to delay for diagnosis \(comparative analyses\), our data also serve to describe the incidence of ectopic pregnancy and the frequency of risk factors and symptoms, in a cohort of patients presenting for very early medication abortion \(<42 days LMP\) and found to have a PUL.](#)

Reviewer #3: Thank you for the opportunity to review this manuscript. This historical cohort study illuminates several important considerations in the management of PULs. The finding that immediate initiation does not lead to increased risks is significant along with the finding of lower medication abortion efficacy. Both of these improve providers' ability to inform patients and participate in improved shared-decision making about how to best approach and unwanted pregnancies classified as a PUL. I have the following suggestions and comments:

Major:

1. My main concern has to do with the finding that no ectopic pregnancies were identified in the same day start group. Your discussion provides good reasoning as to why this may have happened. However, your power sample calculation is confusing since you have unequal groups. You say you need 200 subjects which it appears to be in each group so then say you wanted 500 patients. However, even though you had 452 patients you had unequal groups so you oversampled in the delay group and under in the same day start. Consider a new power calculation that accounts for unequal groups or at the very least provide a post ad hoc power calculation using your results.

[Thank you for this comment. We did not provide all the details of our initial sample size calculation in the manuscript, which has now been updated. We did consider several scenarios of unequal group assignments. Further, we required 200 patients total \(100:100, 125:75 or 150:50\) for the primary analysis \(time to diagnosis\) and 400 patients for the secondary analyses \(binary outcomes\). We hope that our updates to this paragraph have clarified our initial sample size calculation. For further details, please also see response to Reviewer #2, Methods #5 regarding the unequal sample sizes.](#)

2. Do you have information on hCGs? would be helpful to see that data. Was there a beta level in the delay group that was more commonly associated with ectopics? i assume not but would be interesting to see the data or explain why it was not included. Also helpful to know for same day starts if you did anything different with a high quant, e.g. >2000. You show this in Table 1 but don't really provide any information about this. Were most of the ER visits in same day because of need for formal scan?

[According to PPLM protocol, any patient with a PUL who's initial hCG returns >2000 is sent for formal ultrasound. If the formal ultrasound does not demonstrate an IUP \(or probable IUP\) or if the hCG is >3000 the patient must be sent to the ED. This has been clarified in Table 1. Additionally, patients with signs or symptoms concerning for rupturing ectopic are sent to the ED.](#)

[We have collected extensive serum hCG data with clinical correlates and plan to analyze and share that data in a separate manuscript.](#)

3. Results lines 187-190- you say you excluded those with major risk factors but then say that they were more common amongst those that ended up with ectopics. Please clarify. I also think you could consider including the ones with risk factors since it doesn't always mean that they have an ectopic.

[In the whole cohort of patients with PUL, we found that major ectopic risk factors were more common amongst those ultimately found to have an ectopic \(e.g. we confirmed these factors were in fact risk factors\). We excluded patients with major risk factors from all analyses where we compared same-day start to delay-for-diagnosis to make the groups more comparable, because those with major ectopic risk factors were not eligible for same-day start. We sought to compare these management strategies for those at low-risk of ectopic.](#)

Minor comments

1. Precise- I am not sure if you can say that same day start excludes ectopic pregnancy- that seems to imply that it treated it which we can't say for certain. [We changed the word 'excludes' to "rules out" ectopic to remove the implication that mife/miso might treat ectopic.](#)

2. Intro- would help to say incidence of ectopics, and esp under 42 days. [There is limited \(any?\) modern data on the incidence of ectopic pregnancy among patients seeking very early abortion \(<42 days\) that we could identify. This original research sought to provide that incidence data.](#) Also helpful to remind readers of need for immediate identification of ectopics given high risk or morbidity and mortality. [Done](#)

3. Line 55- I would remove persistent PUL since that is not a diagnosis but rather an ongoing classification. [Done](#)

4. Intro- would help to bring up that current mifepristone labeling includes ectopic pregnancy as a contraindication, may also want to include off-label use in your discussion. [We have added mention of mifepristone labeling in the introduction, however word-limits prevent us from discussing off-label use in the discussion.](#)

5. Line 65- i believe there is evidence out there about many patients wanting medical aspiration and would also cite the increasing popularity (see Guttmacher). [Guttmacher citation added.](#)

6. Line 67 you discuss same day start based on varying recommendation. I am familiar with PP MS&Gs but that recommendation is up to 35 days from sure LMP. Would be helpful to specify GA range of the recommendation and then in methods explain why you chose 42. [At the beginning of our study period the PP MS&Gs required that subjects be up to 35 days with sure LMP, then over the course of the 5-year study period the PP MS&Gs changed to allow use of same-day-start up to 42 days with known LMP. We have clarified this in our description of eligibility in the methods section.](#)

7. Discussion lines 271-8 would also include a point as to how your data improved ability to make shared decisions. Some patients may prefer to wait even with lower efficacy while others are willing to take risk of lower efficacy with change it will get the result faster. [Thank you for this suggestion. We have changed the final sentence in our discussion to highlight the utility of our data in facilitating shared decision-making.](#)

8. Discussion regarding how medication abortion may impact tubal abortions- my teaching was that the fallopian tube does not have progesterin receptors so would not be effective. Can you comment on this? [Some data suggests that prostaglandins impact tubal transport and that progesterone and progesterone inhibitors like mifepristone may also exert impact on the smooth muscle function of the fallopian tube. The exact impact of mifepristone and misoprostol on tubal function is incompletely understood. Wånggren K, Stavreus-Evers A, Olsson C, Andersson E, Gemzell-Danielsson K. Regulation of muscular contractions in the human Fallopian tube through prostaglandins and prostagens. Hum Reprod. 2008 Oct;23\(10\):2359-68. doi: 10.1093/humrep/den260. Epub 2008 Jul 11. PMID: 18621753.](#)

STATISTICAL EDITOR COMMENTS:

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

Table 2: As can be seen from this Table, although "Ectopic symptom:Any", "Vaginal bleeding" or "Major risk factor:Any" are each statistically associated with occurrence of EP, there would be high rates of false positives and low rates of PPV were those to be applied in individual cases.

[We agree that our data supports much published evidence, that shows that: 'prior ectopic', 'prior tubal surgery' and 'IUD in place' are risk factors for ectopic pregnancy. Most clinicians would agree that patients with these major risk factors should be managed as if they are 'high-risk' for ectopic and followed very closely. The incidence of these major risk factors amongst pregnant people is also relatively low \(in part because they can impair fertility\).](#)

[We found it much more challenging to clinically and statistically manage the variables of 'vaginal bleeding' and 'any pain'. These symptoms have been shown to be associated with ectopic pregnancy, but are also an expected part of miscarriage and common in normal early pregnancies. PPLM clinical protocols required that in order for subjects to be eligible for same-day start they were supposed to have 'no ectopic symptoms' \(we have added this to the methods\), however, we noted from our data, that in practice, many patients were offered same-day start even if they had some bleeding or pain \(29%\). It is also concerning that 20% of the patients who had an ectopic pregnancy were asymptomatic. This just highlights \(as you point out\), the lack of utility of applying symptomatology to identify individual cases of ectopic.](#)

Table 3: The groups were not randomized and differed significantly in GA by LMP, proportion with uncertain LMP and any ectopic symptoms, so the crude rates of EP outcomes may not be a valid comparison.

[Table 3 only lists the frequency of ectopic pregnancy in each group, it does not include the outcomes of ectopic pregnancies. We have chosen to define 'ectopic' as being 'treated for an ectopic'. We have changed the title of the category to 'diagnosed with ectopic' in this table and describe our definition of ectopic in more detail in the methods section of the text.](#)

[The Reviewer is correct that the groups were not randomized, and there is the potential for confounding. Due to this, we adjusted for the potential confounding factors when possible in our primary analyses. Unfortunately, because there were no ectopic pregnancies in the same-day start group, we could not perform an adjusted regression analysis accounting for these various factors. We have still chosen to show the ectopic pregnancy rates between groups, but we have heavily caveated our results](#)

Table 5: The study is underpowered to discern a difference in serious adverse events due to low counts of adverse events. The study is also underpowered to discern differences in ER visits or non-adherence to follow-up. For the former, the rate among the ER visits for same day start would have to exceed 53% or be < 14% in order to fulfill the usual 80% power and alpha = 0.05, given the sample sizes at hand. Similarly, for non-adherence with follow-up, the same day cohort would have to exceed 33.4% or be < 2.6%, assuming the same power/sample size inputs and a baseline rate = 15.9%. For the safety outcomes, should not the power limitation and include CIs with the point estimates in Table 5.

[We have now included the unadjusted odds ratios with 95% confidence intervals in Table 4 \(previously Table 5\).](#) We added a sentence to the discussion to note that we were underpowered for secondary outcomes when no difference was observed (adverse events, ER visits and non-adherence).

Figs 2, 3: Need to include at time points on the x-axes, the "N" remaining in each cohort. Should include 0,5,10,15, 20 and 25 days at minimum.

[We have updated the figures to include the N remaining in each group.](#)

EDITOR COMMENTS:

General: Please rephrase the statements in your submission to avoid using causal language.

[We have changed the language in the conclusion of the abstract and the beginning of the discussion to remove causal language.](#)

1. The Editors of Obstetrics & Gynecology have increased 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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- * Include clinical trial registration numbers, PROSPERO registration numbers, or URLs at the end of the abstract (if applicable). [Not applicable](#)
- * Name the IRB or Ethics Committee institution in the Methods section (if applicable). [Done](#)
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4. For studies that report on the topic of race or include it as a variable, authors must provide an explanation in the manuscript of who classified individuals' race, ethnicity, or both, the classifications used, and whether the options were defined by the investigator or the participant. In addition, the reasons that race/ethnicity were assessed in the study also should be described (eg, in the Methods section and/or in table footnotes). Race/ethnicity must have been collected in a formal or validated way. If it was not, it should be omitted. Authors must enumerate all missing data

regarding race and ethnicity as in some cases, missing data may comprise a high enough proportion that it compromises statistical precision and bias of analyses by race.

Use "Black" and "White" (capitalized) when used to refer to racial categories. [Done](#) The nonspecific category of "Other" is a convenience grouping/label that should be avoided, unless it was a prespecified formal category in a database or research instrument. If you use "Other" in your study, please add detail to the manuscript to describe which patients were included in that category.

[Race and Hispanic/Latinx ethnicity were self-reported by patients from a list of predefined options including an "other" category. Since 'other' was a predefined formal category, we have kept it in our table. This is now described in the methods section.](#)

[We considered race/ethnicity to be a potential confounder of the treatment group-clinical outcome relationships because provider conscious and unconscious bias are conceptually plausible causal drivers of treatment group allocation and could also be associated with loss to follow up. This is also included in the methods section.](#)

[The frequency of missing data is reported in Table 3.](#)

5. Your submission indicates that one or more of the authors is employed by a pharmaceutical company, device company, or other commercial entity. This must be included as a statement in the Financial Disclosure section on the title page.

[This was clarified via email communication with the editorial staff. The title page has been updated per their recommendations.](#)

6. 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 Methods section of the body text, 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 website outlining the exempt data sets or a letter from a representative of the IRB. In addition, insert a sentence in the 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.

[This study was reviewed by the Partners IRB. It was not considered exempt. This is noted in the manuscript on page 6, line 128 and was also included in our original cover letter.](#)

7. Please submit a complete STROBE checklist with your revision.

[We have attached a revised STROBE checklist with updated page numbers in the margin of the checklist](#)

Responsible reporting of research studies, which includes a complete, transparent, accurate and timely account of what was done and what was found during a research study, is an integral part of good research and publication practice and not an optional extra. Obstetrics & Gynecology supports initiatives aimed at improving the reporting of health research, and we ask authors to follow specific guidelines for reporting randomized controlled trials (ie, CONSORT), observational studies (ie, STROBE), observational studies using ICD-10 data (ie, RECORD), meta-analyses and systematic reviews of randomized controlled trials (ie, PRISMA), harms in systematic reviews (ie, PRISMA for harms), studies of diagnostic accuracy (ie, STARD), meta-analyses and systematic reviews of observational studies (ie, MOOSE), economic evaluations of health interventions (ie, CHEERS), quality improvement in health care studies (ie, SQUIRE 2.0), and studies reporting results of Internet e-surveys (CHERRIES). Include the appropriate checklist for your manuscript type upon submission. Please write or insert the page numbers where each item appears in the margin of the checklist. Further information and links to the checklists are available at http://secure-web.cisco.com/1UvycMz97pl4wdZi4Tk3bo_LgGfCzq18SRaXTeQ-xw4V4bV7MxoFrs7DHOiO419AtJsgSLQKGJAS9kqmbj_tTOpiIXihRpy2NVnEd5P9aqubiCtXaHF5Y5kGMz9AWJJ37MQLI_DjvSFs37mTU5zSqWXF4tSri3J-0f33jD6E94u_j-TXl5OfefynNYbOi9h6UZAbAutCmYqw4820lcj4C8aUQ8ZQN_d9InclJvl-IGxSuU4Dr2rF0raSPG4uSVMaFEOMc2iKk58KiVL5x1zKvtUfP8KStPNFf52v7QN9mvljdG-LLpDeexw5EMvXux-c/http%3A%2F%2Fong.editorialmanager.com In your cover letter, be sure to indicate that you have followed the CONSORT, MOOSE, PRISMA, PRISMA for harms, STARD, STROBE, RECORD, CHEERS, SQUIRE 2.0, or CHERRIES guidelines, as appropriate.

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[Excluding references, the total word count is 5263.](#)

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In addition, the abstract length should follow journal guidelines. The word limit for Original Research articles is 300 words; Reviews is 300 words; Case Reports is 125 words; Current Commentary articles is 250 words; Executive Summaries, Consensus Statements, and Guidelines are 250 words; Clinical Practice and Quality is 300 words; Procedures and Instruments is 200 words. Please provide a word count. [Word count provided \(297 words\).](#)

11. ACOG avoids using "provider." Please replace "provider" throughout your paper with either a specific term that defines the group to which are referring (for example, "physicians," "nurses," etc.), or use "health care professional" if a specific term is not applicable. [Corrections made.](#)

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[We have now included odds ratios where interpretable. For the continuous outcomes \(time to diagnosis & time to complete abortion\), we have left this as a comparison of days with a p-value \(instead of the adjusted odds ratio\) as differences in days to diagnosis is more interpretable for a clinical audience. We have also left the percentages for medication abortion efficacy outcomes as these are more interpretable \(instead of an odds ratio\) to a clinical audience.](#)

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%). [Done](#)

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://secure-web.cisco.com/1pQ-Kdy7utmO_me1oTZ8psWgzYBSyyLnle3itHS0QWGwnVhsuxx09Y3GbT-Mtupp84Uf8C4x-PztVQFz-cDkEygyiWjILU6CHje7jAlwTTiTZzniU0pAzWQCmloVJ5ZKdqShvkQnVIA2XcsO4dRBQwHb_LWZnldwZYuwZP-FEDkPX8UgHHCyDr5ZjHvZQAtpCJTPrYMPDi-vGwDOEmAjjZngK60yUEX0kMKnZ4Evg144c_c4lxDPt8tU9aCxD6vpmxpVbN0iLHCi4PHvO_4MVA2ods_TyW0cGa_oKVNwYGrjnBL2qv9J0QmypoS7Pqx/http%3A%2F%2Fedmqr.ovid.com%2Fong%2Faccounts%2Ftable_checklist.pdf [Done. Formatting, including footnotes, now conforms to journal style.](#)

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[The references have been reformatted in the proper style.](#)

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15. Figures 1-3 may be resubmitted as-is with the revision.
[We have updated these figures in response to the suggestions of other reviewers.](#)

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