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)*

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Date: Nov 20, 2020
To: "Emma Rose Allanson" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-20-2760

RE: Manuscript Number ONG-20-2760

Pretreatment with mifepristone compared with misoprostol alone for the termination of pregnancy following fetal demise between 14 and 28 weeks gestation: a double blind randomized controlled trial

Dear Dr. Allanson:

Your manuscript has been reviewed by the Editorial Board and by special expert referees. Although it is judged not acceptable for publication in Obstetrics & Gynecology in its present form, we would be willing to give further consideration to a revised version.

If you wish to consider revising your manuscript, you will first need to study carefully the enclosed reports submitted by the referees and editors. Each point raised requires a response, by either revising your manuscript or making a clear and convincing argument as to why no revision is needed. To facilitate our review, we prefer that the cover letter include the comments made by the reviewers and the editor followed by your response. The revised manuscript should indicate the position of all changes made. We suggest that you use the "track changes" feature in your word processing software to do so (rather than strikethrough or underline formatting).

Your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Dec 11, 2020, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1:

This started as a well defined double blinded study to be done between 14 & 24 weeks gestation but then was expanded up to 28 weeks. This added confusion to the protocol as now there were some patient (<24 weeks) that were receiving one misoprostol regimen while other patients (24-28 weeks) that were receiving a different regimen. In addition from the table on GA there was one patient that was >28 weeks!

Although the protocol only looked at the time from the initiation of the misoprostol to delivery, the actual termination process started 24-48 hours sooner when the mifepristone was given. It is not surprising that the patients receiving priming from mifepristone used less misoprostol and fewer doses of misoprostol . Perhaps the timing should have started from the mifepristone . Also why was there such variation in mifepristone timing?? The time interval between mifepristone and misoprostol should have been the same for all patients
It is also well known that the gestational age makes significant difference in uterine response to misoprostol.

Therefore would suggest that patients should also have been matched for gestational age or at least window of GA. Although gestational age is reported , we are not given any information about the period of time from fetal demise and termination nor are we told about fetal size. It is also well recognized that after loss of fetal vitality, the fetus will begin to shrink which will also affect response to misoprostol
Finally were patients given the option of D&E? This option is significantly faster and safer in the hands of a skilled obstetrician at < 18 week gestation and in most institutions would be the management of choice

Reviewer #2:

The manuscript is a randomized placebo-controlled trial evaluating the impact of mifepristone prior to misoprostol for the termination of pregnancy following fetal demise in the second trimester. The primary outcome was time from administration of misoprostol to delivery. The study fell well short of its intended patient accrual and part way through, the inclusion criteria were extended up to 28 weeks. However, the authors did find a significant difference in the time to

delivery after misoprostol dosing. The authors include a CONSORT checklist.

1. Introduction: I found the first two paragraphs unclear. I recommend making it clear up front that there may be a difference in the efficacy of adding mifepristone based upon whether or not fetal death has already occurred. Studies exist in the first trimester to support the addition of mifepristone to misoprostol for terminations, but not necessarily for fetal death (Cochrane review). RCTs support use in second trimester terminations. The authors are presenting an RCT in second trimester fetal death. Why is the Chauduri RCT not mentioned here (reference 16)? I recommend some brief mention here of why there might be a difference in success with prior fetal death vs. termination.

2. Methods: Please discuss why the original study design was 14-24 weeks EGA. Is there a physiologic reason? Would that change by extending it to 28 weeks? Why do you think recruitment was so slow? Lines 138-140: why were women taking corticosteroids excluded? Why did the authors use a cut-off of three prior c-sections for exclusion? Did it matter the type of prior c-section? It appears that there were additional inclusion/exclusion criteria (from figure 1) that are not mentioned in the manuscript. Please discuss. Lines 158-160: please briefly indicate why there was a difference in misoprostol dosing.

3. Results: Line 273 and table 2 - the use of 3rd stage oxytocics was not statistically different between the two groups. Lines 242-244: Though the subgroup of those 24-28 weeks was small, did you look to see if there was a difference in this sub-cohort from those pregnancies <24 weeks. Was there an association with gestational age if looked at linearly instead of using a 20 week cut-point? Line 273 would be clearer if stated as "Fewer women in the placebo group received oxytocics in the 3rd stage". However, the p-value for this comparison was NOT statistically significant (Table 2). Lines 277-279: please describe which of the readmissions were in each arm.

4. Discussion: Line 303: Recommend clarifying that the Chaudhuri trial included second and third trimester pregnancy losses and that there was not a sub-group analysis for second trimester only. Line 317-319: why was this your hypothesis? What is the pathophysiology behind it? Line 319-321: In the mifepristone arm, did those patients with a lower progesterone level take longer to respond? Did any of the RCTs in live fetuses look at progesterone levels?
5. Figure 1: Please explain the 557 terminations excluded. Were these patients who underwent surgical termination?
6. Table 1: How is it that one patient had an unknown gestational age if in line 137 an ultrasound was performed in these circumstances?

Reviewer #3:

This interesting paper reports a randomized placebo-controlled study of mifepristone + misoprostol v. placebo + misoprostol for uterine evacuation after fetal death at 14-28 weeks LMP. My specific comments are below:

1. Title: Usually, we do not say that the procedure for uterine evacuation after fetal death is a "termination of Pregnancy" as the fetus is no longer alive. Might be better to use: treatment or management of IUFD...

2. lines 43ff The authors should explain somewhere why they chose the route of miso and the dose

3. The sample size is small, but still the authors really have 4, not 2 groups -- since after a certain GA the change the regimen...it is probably not possible to look at differences also by GA, but the authors should at least comment on this fact-- and maybe include it among the limitations of the study.

4. l.73: interrogated seems the wrong word: studied?

5. The first paragraph lit review uses quite old studies. More recent ones are available that would be much closer to the study being presented here, viz: Contraception:. 2020 Jul;102(1):7-12. doi: 10.1016/j.contraception.2020.02.007. Epub 2020 Mar 3.
Mifepristone pretreatment followed by misoprostol 200 mcg buccal for the medical management of intrauterine fetal death at 14-28 weeks: A randomized, placebo-controlled, double blind trial; Hillary Bracken 1, Nguyen Thi Nhu Ngoc 2, Do Quan Ha 3, et al

6. Lines 76-77 ..."in combination with misoprostol, a prostaglandin analog..." would be better

7. l. 89, change "less" to "few"

8. l. 102: this study examines the possibility that mifepristone can enhance the efficacy of miso; it does not assess the efficacy of mifepristone

9. l. 113: change "considered for" to "offered" or "screened for"

10. ll 118-119: "despite the fact that the majority....were recruited..."

11. It is not clear why the authors chose to analyze estrogen and progesterone levels. There is no evidence that estrogen levels are affected by mifepristone, and the anti-progestin properties are related to terminating very early pregnancy but not to enhancing cervical dilation. The authors might want to note the property of mife in inducing cervical changes -- at least later on in the manuscript.

12. ll158-9: the authors might want to discuss why they chose the regimens they did - altering dose and interval

13. l.197: It would still be interesting to inform the reader of the interval between miso and delivery in the two groups of women in this study

14. l.211 replace "treatment" with "mifepristone"

15. ll.242-3: "The effect of mifepristone on time from misoprostol top delivery did not seem to vary among women with gestations less than 20 weeks compared to those with 20 weeks gestation or more"

16. ll246-7: do you mean time to delivery? (instead of delivery rate?)

17. ll. 252-8: Perhaps this analysis is not very useful: there was variable time from mife to the first dose of miso which cannot be ascribed to the regimen and is not reported for each person. Administrative issues on the ward/hospital usually account for the time of discharge, so this also is not a "fair" analysis.

18. Fig. 2 - there is a notably long tail for the placebo group: please comment on this. It could be very unpleasant for a small group of women! (7/31 with more than 10 hours!)

19. ll. 299 and 300: change "gestation" to "gestational age"

20. ll321-329: shouldn't this be part of the lit review above and not this discussion?

21. ll 356ff the issue of acceptability of treatment is really hard to separate from the circumstances of these women. when you ask about "the experience, " you may be referring to one of the worst moments in their lives: the loss of a desired pregnancy fairly late in gestation. It would be good to comment on this issue, because this situation is entirely unlike asking people how they felt about an elective abortion for an unwanted pregnancy.

22. There are highly detailed tables about patient characteristics -- maybe too detail -- and maybe the number of categories could be decreased. However, there are notably no tables with outcomes.

23. Table 3 needs revision to be clear about the meaning of the question asked (not just an indication of a subject) and what the scale was. The entire question probably should be listed verbatim in the talle.

STATISTICS EDITOR COMMENTS:

Abstract: Needs to conform to our template for RCTs.

Lines 190-193: The description of criteria for sample size calculation is incomplete. Need to specify some measure of variability in the median at 13 hrs and the median at 9.1 hrs (30% reduction).

Fig 1: Were those who declined or who were unable to recruit (n = 26) different from those who consented and who were analyzed? That is, were the cohorts representative or was there potential bias?

Fig 2: Either in the figure itself or in the legend, need to specify the medians and results of stats tests for the two survivor functions.

Tables: The cohorts had N = 34 and 32, so the format for %s should be rounded to nearest integer %, not cited to 0.1% precision.

Table 1: Since the groups were randomized, there is no need to test for statistical differences in baseline characteristics. Ay difference is thought to be due to random chance.

Table 2: Again, the %s should be rounded. The study was not designed, nor is there sufficient power, to generalize the NS

findings re: comparison of maternal complications.

Table 3: Were the scores normally distributed? The sample sizes are modest, do not include all patients and if non normally distributed, formatting as mean value may not be the best representation. If non-normally distributed, should cite as median(Range) and if normally distributed, as mean(range or SD). In either case, the missing data may make this portion of the analysis subject to selection bias.

Need to include a table of the primary outcome, formatted in the same manner in which it was stated in Methods, namely as a comparison of median times. In the same table, should include the secondary outcomes comparing doses and cumulative amounts of misoprostol, while clearly separating the primary from the secondary outcomes.

EDITORIAL OFFICE COMMENTS:

1. The Editors of Obstetrics & Gynecology are seeking to increase transparency around its peer-review process, in line with efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online. Additionally, unless you choose to opt out, we will also be including your point-by-point response to the revision letter. If you opt out of including your response, only the revision letter will be posted. Please reply to this letter with one of two responses:
A. OPT-IN: Yes, please publish my point-by-point response letter.
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2. Obstetrics & Gynecology uses an "electronic Copyright Transfer Agreement" (eCTA). 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.

3. 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).

4. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions. Please access the obstetric data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-obstetrics-data-definitions and the gynecology data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-gynecology-data-definitions. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

5. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Original Research reports should not exceed 22 typed, double-spaced pages (5,500 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and print appendixes) but exclude references.

6. 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).

7. The most common deficiency in revised manuscripts involves the abstract. Be sure there are no inconsistencies between the Abstract and the manuscript, and that the Abstract has a clear conclusion statement based on the results found in the paper. Make sure that the abstract does not contain information that does not appear in the body text. If you submit a revision, please check the abstract carefully.

In addition, the abstract length should follow journal guidelines. The word limit for Original Research articles is 300 words. Please provide a word count.

8. 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.

9. 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.

10. 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.

11. 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%").

12. 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.

13. 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 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 at the Clinical Guidance page at https://www.acog.org/clinical (click on "Clinical Guidance" at the top).

14. Figure 1: Please check n values between those assessed for eligibility and the randomization (110 less the exclusions is 65, not 66). Please upload as a figure file on Editorial Manager.
Figure 2: Please upload as a figure file on Editorial Manager.

When you submit your revision, art saved in a digital format should accompany it. If your figure was created in Microsoft Word, Microsoft Excel, or Microsoft PowerPoint formats, please submit your original source file. Image files should not be copied and pasted into Microsoft Word or Microsoft PowerPoint.

When you submit your revision, art saved in a digital format should accompany it. Please upload each figure as a separate file to Editorial Manager (do not embed the figure in your manuscript file).

If the figures were created using a statistical program (eg, STATA, SPSS, SAS), please submit PDF or EPS files generated directly from the statistical program.

Figures should be saved as high-resolution TIFF files. The minimum requirements for resolution are 300 dpi for color or black and white photographs, and 600 dpi for images containing a photograph with text labeling or thin lines.

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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. 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 Dec 11, 2020, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

John O. Schorge, MD
Associate Editor, Gynecology

2019 IMPACT FACTOR: 5.524
2019 IMPACT FACTOR RANKING: 6th out of 82 ob/gyn journals

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17th December, 2020

Dear Editor,

Re: “Pretreatment with mifepristone compared with misoprostol alone for the termination of pregnancy following fetal demise between 14 and 28 weeks gestation: a double blind randomized controlled trial”

Thank you for the reviews. We have addressed each comment below and resubmitted our manuscript for consideration.

We look forward to hearing the outcome of this submission,

Dr Emma Allanson
MBBS, MPHTM, FRANZCOG, PHD

On behalf of co-authors
Sean Copson, Katrina Spilsbury, Sonya Criddle, Belinda Jennings, Dorota Doherty, Antonia Wong, and Jan Dickinson

REVIEWER COMMENTS:

Reviewer #1:

This started as a well defined double blinded study to be done between 14 & 24 weeks gestation but then was expanded up to 28 weeks. This added confusion to the protocol as now there were some patient (<24 weeks) that were receiving one misoprostol regimen while other patients (24-28 weeks) that were receiving a different regimen. In addition from the table on GA there was one patient that was >28 weeks!

We thank the reviewer for the comments. The trial amendment is a potential limitation and we have further addressed this in the discussion (below, page 18). The one patient referred to was 28 weeks exactly and so met trial inclusion criteria (see table 1)

"Equally the need for a protocol amendment to increase capacity for recruitment is potentially confounding given the different treatment regimen applied to patients ≥ 24 weeks gestation, however this is likely reflective of real world practice." (Line 389-391)

Although the protocol only looked at the time from the initiation of the misoprostol to delivery, the actual termination process started 24-48 hours sooner when the mifepristone was given. It is not surprising that the patients receiving priming from mifepristone used less misoprostol and fewer doses of misoprostol . Perhaps the timing should have started from the mifepristone . Also why was there such variation in mifepristone timing?? The time interval between mifepristone and misoprostol should have been the same for all patients
It is also well known that the gestational age makes significant difference in uterine response to misoprostol. Therefore would suggest that patients should also have been matched for gestational age or at least window of GA.

While it would be ideal to have the same timing for each patient from mifepristone / placebo to misoprostol, this was unfortunately not pragmatic. In our setting the mifepristone / placebo is given as an outpatient and then admission is arranged in the 24-48 hour period following, pending hospital resources / patient specific circumstances. We were however interested in the time from misoprostol to delivery (as has previously been looked at following mifepristone priming in live fetal termination and this is the main factor determining the hospital inpatient stay) given that the role of mifepristone in termination following fetal demise has largely not been established in prospective randomised trial. Patients were analysed based on gestational windows.

Although gestational age is reported, we are not given any information about the period of time from fetal demise and termination nor are we told about fetal size. It is also well recognized that after loss of fetal vitality, the fetus will begin to shrink which will also affect response to misoprostol

We thank the reviewer for this point. While we agree that fetal size may change following demise, it was not possible to determine the time from demise to presentation for every woman. The blinded randomisation of the trial would account for this between groups.

Finally were patients given the option of D&E? This option is significantly faster and safer in the hands of a skilled obstetrician at < 18 week gestation and in most institutions would be the management of choice

We thank the review for this comment. They were not given this option as the management of choice in our unit (and many similar to it in our setting) is a medical rather than a surgical approach.

Reviewer #2:

The manuscript is a randomized placebo-controlled trial evaluating the impact of mifepristone prior to misoprostol for the termination of pregnancy following fetal demise in the second trimester. The primary outcome was time from administration of misoprostol to delivery. The study fell well short of its intended patient accrual and part way through, the inclusion criteria were extended up to 28 weeks. However, the authors did find a significant difference in the time to delivery after misoprostol dosing. The authors include a CONSORT checklist.

1. Introduction: I found the first two paragraphs unclear. I recommend making it clear up front that there may be a difference in the efficacy of adding mifepristone based upon whether or not fetal death has already occurred. Studies exist in the first trimester to support the addition of mifepristone to misoprostol for terminations, but not necessarily for fetal death (Cochrane review). RCTs support use in second trimester terminations. The authors are presenting an RCT in second trimester fetal death. Why is the Chauduri RCT not mentioned here (reference 16)? I recommend some brief mention here of why there might be a difference in success with prior fetal death vs. termination.

We thank the reviewer for the point and have updated the first two paragraphs to more clearly delineate our point, outlined below. (Lines 74-100)

"The use of mifepristone across the gestational spectrum has increased since the first clinical trials in the 1980's interrogating its use as an abortifacient in early pregnancy(1). Mifepristone (a competetive progesterone antagonist) primes the myometrium and cervix to respond to prostaglandins and is therefore used in combination with a prostaglandin analogue (e.g. misoprostol). Mifepristone has been safely and efficaciously used in medical termination of pregnancy in the first and second trimesters(2, 3)

Several randomized trials have demonstrated the usefulness of mifepristone prior to prostaglandin use for second trimester termination where the fetus is alive. Mifepristone priming results in a shortened induction to abortion interval and a reduced dosage of prostaglandins required to achieve delivery(3-6). There are fewer data available on the role of mifepristone in termination of pregnancy following fetal demise and the relevance of blocking the effect of residual progesterone in a non-viable pregnancy is unclear. Two randomized controlled trials completed since commencement of this study demonstrated a reduction in the time to delivery following misoprostol administration after mifepristone priming in the setting of fetal death in the second and third trimester(7, 8). The randomized trial of Chaudhuri and Datta (14) investigated women with a fetal death after 20 weeks

gestation (median gestation 32 weeks) using a regimen of 50-100 mcg vaginal misoprostol 6-hourly for a maximum of 4 doses, and reported a significant reduction in delivery interval in those women randomized to mifepristone compared with placebo. The recent trial of Bracken et al (15) used 200 mcg buccal misoprostol 3-hourly for a maximum of 16 doses in pregnancies of 14-28 weeks gestation with a significant reduction in the fetal expulsion time for the women receiving mifepristone priming. There are also several cohort studies supporting the use of misoprostol following mifepristone priming in the setting of fetal death after the first trimester."

2. Methods: Please discuss why the original study design was 14-24 weeks EGA. Is there a physiologic reason? Would that change by extending it to 28 weeks? Why do you think recruitment was so slow? Lines 138-140: why were women taking corticosteroids excluded? Why did the authors use a cut-off of three prior c-sections for exclusion? Did it matter the type of prior c-section? It appears that there were additional inclusion/exclusion criteria (from figure 1) that are not mentioned in the manuscript. Please discuss. Lines 158-160: please briefly indicate why there was a difference in misoprostol dosing.

We have amended the methods to explain the reason for the gestation, which was based on usual practice. The methods now read:

"The initial gestational age inclusion criteria was determined by usual practice in our unit for the management of fetal demise less than 24 weeks gestation, however due to slow recruitment, a protocol amendment was made and approved on the 10th December 2013" (Lines 115-119)

The reasons for slow recruitment may be related to system changes within the region and patients being managed at hospitals outside of our service.

Mifepristone is contraindicated in patients on long term corticosteroids in Australia (as determined by the Australian Therapeutic Drug Administration) and this is written in the manufacturer guidelines in our country. Given the cohort data showing an increased risk of uterine rupture with previous cesarean and medical interruption of pregnancy, more than 3 previous cesarean sections was considered a relative contraindication to mifepristone / misoprostol in our unit.

We have updated the methods to read:

"Women were excluded if they were taking corticosteroids (see below), had a documented allergy to misoprostol or mifepristone, had a history of more than three previous cesarean sections, presented with ruptured membranes, presented in spontaneous labour, were non-English speaking or were unable to provide written consent. Mifepristone is contraindicated in patients on long term corticosteroids in Australia (as determined by the Australian Therapeutic Drug Administration) and this is written in the manufacturer guidelines in our country. We recognise that in other countries mifepristone may be "Offered with precaution"(10)." (Lines 145-152)

Women were given misoprostol according to unit protocol, which varies above and below 24 weeks. We have amended the methods to explain this

"According to standard unit protocols, women between 14 and 24 weeks received 400 micrograms of misoprostol 6 hourly vaginally and women between 24 and 28 weeks were given 200 micrograms 4 hourly vaginally." (Lines 169-171)

3. Results: Line 273 and table 2 - the use of 3rd stage oxytocics was not statistically different between the two groups. Lines 242-244: Though the subgroup of those 24-28 weeks was small, did you look to see if there was a difference in this sub-cohort from those pregnancies <24 weeks. Was there an association with gestational age if looked at linearly instead of using a 20 week cut-point? Line 273 would be clearer if stated as "Fewer women in the placebo group received oxytocics in the 3rd stage". However, the p-value for this comparison was NOT statistically significant (Table 2). Lines 277-279: please describe which of the readmissions were in each arm.

Line 261-262 updated "Although not significant, women in the placebo group were more likely not to receive oxytocics in the 3rd stage, and the reasons for this were not recorded."

Given the small size of the groups, we did no undertake a subgroup analysis for less and more than 24 weeks.

Line 265-268 have been updated to read "Of the five women readmitted, four were for retained products of conception requiring suction curettage in operating room (four in the placebo group and one in the mifepristone group), and one was for endometritis requiring intravenous antibiotics (in the mifepristone group)."

4. Discussion: Line 303: Recommend clarifying that the Chaudhuri trial included second and third trimester pregnancy losses and that there was not a sub-group analysis for second trimester only. Line 317-319: why was this your hypothesis? What is the pathophysiology behind it? Line 319-321: In the mifepristone arm, did those patients with a lower progesterone level take longer to respond? Did any of the RCTs in live fetuses look at progesterone levels?

We have clarified further and line 293 onwards now reads:

"Our trial adds to the data of the two existing randomized controlled trials(7, 8). Chauduri and Datta randomized 110 women with a fetal demise greater than 20 weeks (including those in the third trimester), to 200 mg of mifepristone followed by a misoprostol regimen of 100 micrograms vaginally 6 hourly in women less than 26 weeks and 50 micrograms vaginally six hourly in women greater than 26 weeks. Despite a differing misoprostol regimen, they also found a reduction in time to delivery of the fetus after commencement of misoprostol (16.3 hours compared with 9.8 hours when mifepristone used, p<0.001)(7). A further randomized trial was published in 2020 by Bracken et al(8) using 200 mcg buccal misoprostol every 3 hours following mifepristone pretreatment at a gestational range of 14-28 weeks. The authors reported completion of the delivery process by 48 hours in 82.2% of women in the mifepristone arm compared with 81.4% in the placebo trial arm (p=0.887), however the median duration of delivery was significantly shorter in the mifepristone arm (7 hours compared with 12 hours, p <0.001). In a cohort of 96 patients, Wagaarachchi and colleagues found mifepristone prior to

misoprostol for induction following fetal demise after 24 weeks to result in an average time to delivery of 8.5 hours, although there was no control group(12). A 2007 retrospective study comparing mifepristone and misoprostol with misoprostol alone (with a variety of doses) in fetal demise found a reduction in time to delivery in the mifepristone group only in gestational ages 21-25 weeks(13). In their retrospective cohort study, Fyfe and Murray report a shorter duration of labor with the use of mifepristone prior to induction after 20 weeks, although it should be noted that only 20% of cases in the mifepristone treatment group had experienced a fetal demise prior to induction(14). In addition to this, a non-blinded trial conducted in Nepal showed that the use of mifepristone after a fetal demise from 20 weeks gestation onwards decreased the dose of misoprostol required but not the total time from commencement of misoprostol to delivery(15). Two further prospective but non-blinded randomized trials in women greater than 28 weeks gestation with a fetal demise demonstrated a shorter time to delivery and less doses of misoprostol needed after use of mifepristone(16, 17)."

We thank the reviewer for the comments about mifepristone. We did not have any difference in progesterone to be able to analyse time to response. We have however updated the discussion to the following

"Prior to conducting this trial, and given that the existing data for the use of mifepristone at similar gestations was in pregnancies with a live fetus, and considering the anti-progesterone action of mifepristone we hypothesized that the potential change in maternal serum progesterone levels after the occurrence of a fetal demise may impact on the efficacy of mifepristone" (Line 323-325)

5. Figure 1: Please explain the 557 terminations excluded. Were these patients who underwent surgical termination?

These were patients having a termination of pregnancy (medical or surgical) where the termination was planned and the fetus alive. We have updated the flow chart to read "Planned abortions (n=557)"

6. Table 1: How is it that one patient had an unknown gestational age if in line 137 an ultrasound was performed in these circumstances?

This was a patient who withdrew post randomisation and her medical record was incomplete.

Reviewer #3:

This interesting paper reports a randomized placebo-controlled study of mifepristone + misoprostol v. placebo + misoprostol for uterine evacuation after fetal death at 14-28 weeks LMP. My specific comments are below:

1. Title: Usually, we do not say that the procedure for uterine evacuation after fetal death is a "termination of Pregnancy" as the fetus is no longer alive. Might be better to use: treatment or management of IUFD...

We thank the reviewer for the point, however we have used termination of pregnancy in line with other similar literature (e.g. Cochrane review which states "To assess, from clinical trials, the effectiveness and safety of different medical treatments for the termination of non-viable pregnancies.")

2. lines 43ff The authors should explain somewhere why they chose the route of miso and the dose

This is institutional protocol and the introduction has been updated to read:

"Our institution has typically used vaginal misoprostol following mifepristone priming following a randomized trial(9) and wished to extend this experience to women with a fetal demise." (lines 102-104)

As well as this the methods have been updated to read "According to standard unit protocols, women between 14 and 24 weeks received 400 micrograms of misoprostol 6 hourly vaginally and women between 24 and 28 weeks were given 200 micrograms 4 hourly vaginally." (Lines 169-171)

3. The sample size is small, but still the authors really have 4, not 2 groups -- since after a certain GA the change the regimen...it is probably not possible to look at differences also by GA, but the authors should at least comment on this fact-- and maybe include it among the limitations of the study.

We thank the reviewed for the comment and have updated the discussion to read

"Equally the need for a protocol amendment to increase capacity for recruitment is potentially confounding given the different treatment regimen applied to patients ≥ 24 weeks gestation, however this is likely reflective of real world practice." (Lines 389-391)

4. l.73: interrogated seems the wrong word: studied?

We thank the reviewer for the comment however we have not changed the word

5. The first paragraph lit review uses quite old studies. More recent ones are available that would be much closer to the study being presented here, viz: Contraception:. 2020 Jul;102(1):7-12. doi: 10.1016/j.contraception.2020.02.007. Epub 2020 Mar 3.
Mifepristone pretreatment followed by misoprostol 200 mcg buccal for the medical management of intrauterine fetal death at 14-28 weeks: A randomized, placebo-controlled, double blind trial; Hillary Bracken 1, Nguyen Thi Nhu Ngoc 2, Do Quan Ha 3, et al

We thank the reviewer for bringing this to our attention. The introduction has been updated to read

"Several randomized trials have demonstrated the usefulness of mifepristone prior to prostaglandin use for second trimester termination where the fetus is alive. Mifepristone priming results in a shortened induction to abortion interval and a reduced dosage of prostaglandins required to achieve

delivery(3-6). There are fewer data available on the role of mifepristone in termination of pregnancy following fetal demise and the relevance of blocking the effect of residual progesterone in a non-viable pregnancy is unclear. Two randomized controlled trials completed since commencement of this study demonstrated a reduction in the time to delivery following misoprostol administration after mifepristone priming in the setting of fetal death in the second and third trimester(7, 8). The randomized trial of Chaudhuri and Datta (14) investigated women with a fetal death after 20 weeks gestation (median gestation 32 weeks) using a regimen of 50-100 mcg vaginal misoprostol 6-hourly for a maximum of 4 doses, and reported a significant reduction in delivery interval in those women randomized to mifepristone compared with placebo. The recent trial of Bracken et al (15) used 200 mcg buccal misoprostol 3-hourly for a maximum of 16 doses in pregnancies of 14-28 weeks gestation with a significant reduction in the fetal expulsion time for the women receiving mifepristone priming. There are also several cohort studies supporting the use of misoprostol following mifepristone priming in the setting of fetal death after the first trimester."

6. Lines 76-77 ..."in combination with misoprostol, a prostaglandin analog..." would be better

Line changed to "in combination with a prostaglandin analogue (e.g. misoprostol)" (Line 77-78)

7. l. 89, change "less" to "few"

Line changed to "there are fewer data" (Line 85)

8. l. 102: this study examines the possibility that mifepristone can enhance the efficacy of miso; it does not assess the efficacy of mifepristone

Line has been changed to "colleagues found mifepristone prior to misoprostol for induction following fetal demise after 24 weeks to result in an average time to delivery of 8.5 hours" (Lines 307-308)

9. l. 113: change "considered for" to "offered" or "screened for"

Line changed to "Western Australia were screened for enrolment" (Line 115)

10. ll 118-119: "despite the fact that the majority....were recruited..."

Line changed to "despite the fact that the majority" (Line 122)

11. It is not clear why the authors chose to analyze estrogen and progesterone levels. There is no evidence that estrogen levels are affected by mifepristone, and the anti-progestin properties are related to terminating very early pregnancy but not to enhancing cervical dilation. The authors might want to note the property of mife in inducing cervical changes -- at least later on in the manuscript.

We thank the reviewer for the comments. We have a secondary arm of the trial (results to be published elsewhere) that looks at the range of normal E2 and progesterone levels in pregnancy,

which is why we added the E2. At the time of planning this trial, there were no other RCTs assessing the role of mifepristone in fetal demise and so we felt it important to look at the progesterone levels such that if the trial was not positive in its results, low levels may be one explanation as to why. We have updated the methods to read

"A secondary arm of this trial (with the results to be published separately) was to assess the circulating progesterone and estrogen levels in the trial patients as well as a cohort of women undergoing induced abortion of pregnancy with a live fetus. The aim of this was twofold; one to consider whether the efficacy of mifepristone is related to the concentration of progesterone in the setting of fetal demise, and to analyse the usual range of both progesterone and estrogen levels in pregnancy." (Lines 134-140)

12. ll158-9: the authors might want to discuss why they chose the regimens they did - altering dose and interval

We thank the reviewer for this comment. Women were given misoprostol according to unit protocol, which varies above and below 24 weeks. We have amended the methods to explain this

"According to standard unit protocols, women between 14 and 24 weeks received 400 micrograms of misoprostol 6 hourly vaginally and women between 24 and 28 weeks were given 200 micrograms 4 hourly vaginally." (Lines 169-171)

13. l.197: It would still be interesting to inform the reader of the interval between miso and delivery in the two groups of women in this study

Thankyou, this can be found on page 11

"The median time from misoprostol to delivery in the placebo group was 10.5 hours, compared to 6.8 hours in the treatment group (HR 2.41 95% CI 1.39-4.17, p=0.002) (Figure 2). "

14. l.211 replace "treatment" with "mifepristone"

We thank the review for the comment, however in order to keep consistent with the rest of the manuscript, we have left this as treatment

15. ll.242-3: "The effect of mifepristone on time from misoprostol top delivery did not seem to vary among women with gestations less than 20 weeks compared to those with 20 weeks gestation or more"

This has been changed (Lines 235-237)

16. ll246-7: do you mean time to delivery? (instead of delivery rate?)

Yes and this has been changed (Line 239)

17. ll. 252-8: Perhaps this analysis is not very useful: there was variable time from mife to the first dose of miso which cannot be ascribed to the regimen and is not reported for each person. Administrative issues on the ward/hospital usually account for the time of discharge, so this also is not a "fair" analysis.

We thank the review for this comment. We agree that the administrative issues are likely the cause of this, however we felt it was important to comment on this for the reasons addressed in the discussion (copied below)

"While there was an improvement in the time from misoprostol to delivery in the treatment group, there was no significant differences between the two groups in either the total amount of time spent in hospital, or the time from commencing misoprostol to leaving hospital. In our unit, this is likely a function of most admissions historically being overnight (which is borne out in the admissions time in both groups being just over 24 hours) to allow for the perinatal care processes following a termination of pregnancy (pastoral care, the taking of memento photos and prints for parents, time spent with the baby). However, the significant reduction in delivery time would plausibly allow for termination of pregnancy in cases like those described here to be done as a day case without the need for overnight hospital admission, as long as one could complete all the other processes either during that time or in an outpatient capacity."

18. Fig. 2 - there is a notably long tail for the placebo group: please comment on this. It could be very unpleasant for a small group of women! (7/31 with more than 10 hours!)

We have highlighted this further in the discussion

"However, the significant reduction in delivery time (as well as the difference in the number of women taking up to 24 hours to deliver)" (Line 358-359)

19. ll. 299 and 300: change "gestation" to "gestational age"
This has been changed (Line 256)

20. ll321-329: shouldn't this be part of the lit review above and not this discussion?

We thank the reviewer for this comment. The lit review has been updated to read:

"Several randomized trials have demonstrated the usefulness of mifepristone prior to prostaglandin use for second trimester termination where the fetus is alive. Mifepristone priming results in a shortened induction to abortion interval and a reduced dosage of prostaglandins required to achieve delivery(3-6). There are fewer data available on the role of mifepristone in termination of pregnancy following fetal demise and the relevance of blocking the effect of residual progesterone in a non-viable pregnancy is unclear. Two randomized controlled trials completed since commencement of this study demonstrated a reduction in the time to delivery following misoprostol administration after mifepristone priming in the setting of fetal death in the second and third trimester(7, 8). The randomized trial of Chaudhuri and Datta (14) investigated women with a fetal death after 20 weeks gestation (median gestation 32 weeks) using a regimen of 50-100 mcg vaginal misoprostol 6-hourly

for a maximum of 4 doses, and reported a significant reduction in delivery interval in those women randomized to mifepristone compared with placebo. The recent trial of Bracken et al (15) used 200 mcg buccal misoprostol 3-hourly for a maximum of 16 doses in pregnancies of 14-28 weeks gestation with a significant reduction in the fetal expulsion time for the women receiving mifepristone priming. There are also several cohort studies supporting the use of misoprostol following mifepristone priming in the setting of fetal death after the first trimester."

21. ll 356ff the issue of acceptability of treatment is really hard to separate from the circumstances of these women. when you ask about "the experience, " you may be referring to one of the worst moments in their lives: the loss of a desired pregnancy fairly late in gestation. It would be good to comment on this issue, because this situation is entirely unlike asking people how they felt about an elective abortion for an unwanted pregnancy.

We agree and thank the reviewer for the comment. We have amended the discussion on this to more clearly highlight this point

"Women who received misoprostol had a better opinion of the procedure than those that received placebo, although neither rate it well. This is a not insignificant finding, although we are limited in our ability to comment on the reasons both the ratings and the differences were observed in our trial. We appreciate the clinical circumstance of an unexpected fetal demise may have contributed significantly to this. Moreover, some evidence suggests that women's experience of a medical (as opposed to surgical) termination of pregnancy worsens with increasing gestational age(24) and this may be reflected here in the scores in both groups of women. It is also plausible that the relatively short time to delivery in the mifepristone group goes some way to account for the improved perception of the procedure in these women. Perception scores in all four categories in both groups of women were worse in our trial compared to the sequential mifepristone misoprostol trial in the second trimester of Dickinson et al(17), although with the notable difference of planned medical termination of pregnancy in that trial compared to the occurrence of unexpected fetal demise in our group of women. The fact that women in our trial did not have a particularly good impression of control nor want to recommend the procedure to a friend may be a function of the clinical scenario these women are experiencing." (Line 364-380)

22. There are highly detailed tables about patient characteristics -- maybe too detail -- and maybe the number of categories could be decreased. However, there are notably no tables with outcomes.

We thank the reviewer for this comment. We have not made any changes at this stage.

23. Table 3 needs revision to be clear about the meaning of the question asked (not just an indication of a subject) and what the scale was. The entire question probably should be listed verbatim in the talle.

We thank the reviewer. This is written out in the methods, copied below

"At time of discharge, patients completed a four question visual analogue questionnaire (used in previous similar randomized trials conducted by our group(17)) with answers obtained using a visual analogue ruler scaled from 0 to 10, with 0 perceived as "much better than expected" and 10 as "much worse than expected", for the following questions: what did you think of the procedure?, how would you rate your pain during the procedure?, would you recommend this method of termination to a friend in a similar situation?, how much control did you feel you had?"

STATISTICS EDITOR COMMENTS:

Abstract: Needs to conform to our template for RCTs.

This has been updated

Lines 190-193: The description of criteria for sample size calculation is incomplete. Need to specify some measure of variability in the median at 13 hrs and the median at 9.1 hrs (30% reduction).

We have now included the interquartile range around the expected median in the methods sections as requested. The methods section was modified as follows:

"Based on a median duration of labor with misoprostol alone in the second trimester of 13 (IQR, 11-22) hours[15], a sample size of 116 per group was calculated to achieve 80% power to detect a 30% reduction in the median duration of labor (equivalent to 9.1 hours) at a 0.05 significance level while using a two-sided log rank test (PASS 2008 for Windows, Kaysville Utah)."

However, we note that sample size calculation for the log rank test using median survival times does not require input of any measure of variability. We used the Lakatos (1988) method which is based on a Markov model that yields the asymptotic mean and variance of the logrank statistic under very general conditions.

Lakatos E. Sample sizes based on the log-rank statistic in complex clinical trials. Biometrics. 1988 Mar;44(1):229-41.

Fig 1: Were those who declined or who were unable to recruit (n = 26) different from those who consented and who were analyzed? That is, were the cohorts representative or was there potential bias?

We thank the reviewer for this comment however we have no data available on these women.

Fig 2: Either in the figure itself or in the legend, need to specify the medians and results of stats tests for the two survivor functions.

The median survival time for placebo group was 10.5 (IQR 8.0-15.0) hours and for the mifepristone group was 6.8 (IQR 5.3 – 10.6) hours. Log rank test for equality of survivor function p-value was 0.0012.

This information has now been added to Fig 2.

Tables: The cohorts had N = 34 and 32, so the format for %s should be rounded to nearest integer %, not cited to 0.1% precision.

We disagree with the reviewer that percentage values should all be rounded to the nearest integer in the Tables. We followed Coles (2015) recommendation that is also cited for use by the Equator network (Enhancing the Quality and Transparency of Health Research https://www.equator-network.org/). Our understanding of the recommendation is that percentage values be presented to 0.1% precision where the range of difference between percentage values being reported is less than 10%. As some percentage values in Tables meet this definition, we originally chose more precision. However, as the frequencies are also presented, a reader can calculate a more precise percentage if required. So, we have modified Tables 1 and 2 as requested by the reviewer.

However, we have not changed Table 3, with the recommendation being "rounding should not blur the differences between them". If we rounded to integer values, then we could not distinguish between some of the means.

Cole TJ. Too many digits: the presentation of numerical data. Arch Dis Child. 2015;100(7):608-609.

Table 1: Since the groups were randomized, there is no need to test for statistical differences in baseline characteristics. Any difference is thought to be due to random chance.

We have removed p-values

Table 2: Again, the %s should be rounded. The study was not designed, nor is there sufficient power, to generalize the NS findings re: comparison of maternal complications.

Percentage value have been rounded.

Table 3: Were the scores normally distributed? The sample sizes are modest, do not include all patients and if non normally distributed, formatting as mean value may not be the best representation. If non-normally distributed, should cite as median (Range) and if normally distributed, as mean (range or SD). In either case, the missing data may make this portion of the analysis subject to selection bias.

We thank the reviewer for this suggestion. Normal quantile plots and Shapiro-Wilk tests indicated that two of the variables representing patient responses may show some degree of non-normality. To facilitate interpretation of the central tendency with, we have added standard deviations, medians and IQR and reported the Wilcoxon rank sum test p-value in Table 3.

The methods section has also been modified as follows:

"Equality of categorical and normally distributed continuous variables by treatment group were assessed using two-sided Fisher's exact tests and t-tests respectively on all available data for each variable. Where normality was in doubt, medians and interquartile range were reported and Wilcoxon rank-sum tests performed." (Lines 205-209)

Need to include a table of the primary outcome, formatted in the same manner in which it was stated in Methods, namely as a comparison of median times. In the same table, should include the secondary outcomes comparing doses and cumulative amounts of misoprostol, while clearly separating the primary from the secondary outcomes.

We thank the reviewer for this comment. As this is included in the body of the results, as well as now that we have amended Figure 2 to include the median times to delivery, we have not duplicated this information in an additional table.

EDITORIAL OFFICE COMMENTS:

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

A. OPT-IN: Yes, please publish my point-by-point response letter.