COMPARISON OF MIFEPRISTONE PLUS MISOPROSTOL WITH MISOPROSTOL ALONE FOR FIRST TRIMESTER MEDICAL ABORTION: A SYSTEMATIC REVIEW & META-ANALYSIS PROTOCOL

Tariku Shimels, MSc1, Mebratu Abraha, MPH1, Mensur Shafie, MSc2, Lemi Belay, MD.3, Melsew Getnet, MPH1

ABSTRACT

BACKGROUND: Original clinical trials have demonstrated that the combined mifepristone plus misoprostol has a marked effectiveness on first trimester abortion practices compared to the misoprostol alone regimen. However, there is no clear evidence if this effect holds consistent direction for all main outcomes and, whether subsequent side effects are minimal or not. This review is intended to provide aggregated evidence for this question through comparison of the respective regimens based on findings reported by previous randomized control trials.

OBJECTIVE: The aim of this review is to compare mifepristone plus misoprostol combined regimen with misoprostol alone in medical abortion of first trimester pregnancy.

METHODS: An internet based search of different engines will be undertaken to identify articles on the proposed topic. Using text words contained in the titles and abstracts of relevant articles, a full search of PubMed/ Medline, Cochrane, EMBASE, WHO international clinical Trial registry platform and google scholar will be made. All English-based articles published earlier to December 2021 on human subjects will be included. Studies which fulfil the inclusion criteria will be selected, appraised and assessed for methodological quality by two independent reviewers. Data on participants, study methods, interventions, and outcomes will be abstracted. Included studies will be pooled for meta-analysis. Results will be reported in either of a risk or ratio at 95% confidence intervals.

PROSPERO Registration Number: CRD42019134213

KEYWORDS: First Trimester, Mifepristone plus Misoprostol, Medical abortion, Misoprostol alone

(The Ethiopian Journal of Reproductive Health; 2022; 16;45-51)
INTRODUCTION

Abortion is a medical phenomenon which requires either a drug or non-drug based intervention.\(^1\) Causes for seeking abortion services may vary among different groups. A significant number of pregnant women appear to visit health facilities for emergency management of induced abortion.\(^2\) Whereas, those women with unwanted pregnancy and having an intention to stop at early weeks of gestation are one inevitable aspect of this group, attendance following an intrauterine foetal death or viability failure, due to various causes, is frequently mentioned.\(^3-5\)

Medical management (procedure that institute drugs) alone or in combination with surgical alternatives is a strategy to manage emergency abortions.\(^6,7\) It was reported that medication based abortion reduces the occurrence of complications. The drugs can be self-administered with a considerably high level of success rate.\(^7,8\) In the US alone, medication abortion using mifepristone and misoprostol is practiced by 92% of the providers.\(^6\) Similarly, about 75% of the providers in Canada and 98% of the providers in the US offered medication abortion to people less than 18 years of age.\(^6\)

Endogenous substances with property of uterine contractility include prostaglandins (PGE2 and PGF2a) and their synthetic analogues (gemeprost, sulprostone, meteneprost and misoprostol), cytotoxic drugs as methotrexate, the anti-progesterone mifepristone and aromatic organic compounds as ethacridine lactate.\(^9,10\) It is widely accepted that a remarkable possibility of attaining complete expulsion of conceptus tissue occurs when prostaglandin analogues and mifepristone are used together.\(^11,12\) The introduction of these agents in the maternal healthcare has also brought about a breakthrough to preventing premature mortality and pregnancy related maternal complications.\(^13\)

The effect of prostaglandins alone and combined agents in the termination of first trimester of pregnancy was evaluated in a systematic review by Kulier et al.\(^14\) Four out of five studies included in the review compared combinations other than mifepristone and misoprostol against misoprostol alone on successful abortion and side effects. Though an updated version of the same review was published in 2011,\(^15\) the evaluation of recent trials has been sought as an added merit to gain a precise insight on the conditions, such as missed abortion, effect difference by fetal heartbeat status, secondary outcomes in addition to nausea and vomiting, as well as pooled effect size estimates for studies on complete abortion. The two regimens have important pharmacokinetic and pharmacodynamics properties making them drugs of choice in the maternal healthcare. Among all prostaglandin analogues which contract the uterus and ripen the cervix, Misoprostol is the most widely used agent which is also orally active, stable at room temperature, and relatively inexpensive.\(^16,17\) In addition, it is well absorbed following oral, vaginal, buccal or sublingual administration and has a proven safety record.\(^16\) Advances in the reproductive health and gynecology practices have devised the administration of mifepristine, a progesterone receptor antagonist, prior to misoprostol to attain effective termination of pregnancy.\(^18\) This agent substantially blocks the P receptors (progesterone receptors) in the placenta, resulting in the cessation of the uterine implantation.\(^19\) Combination of mifepristone, even at a low-dose with misoprostol is highly effective and acceptable as a self-administered abortifacient recommended as the preferred combination regimen.\(^19,20\)

An original clinical trial\(^20\) and reviews\(^21-23\) showed that the combination regimen of mifepristone and misoprostol has resulted in higher proportion of success rate as compared to the misoprostol alone in second trimester abortions. Considerably, it remains to be a question of thorough investigation whether termination of first trimester pregnancy with mifepristone followed by misoprostol would show a better outcome when compared with misoprostol alone. The fact that proportion of unsafe abortions is reported to be higher in the developing than developed nations (49.5% vs. 12.5%),\(^24\) and
the growing number of first trimester pregnancy abortions globally most being adolescents in poor income countries, demands for rich evidence on safe management strategies. Rate of successful abortion was also reported to vary with timing of subsequent misoprostol administration following mifepristone. The systematic reviews conducted, so far, have significant variation in terms of the designs employed, drugs considered, target population factors as well as statistical measures applied by original studies, consequently, ending with diverse conclusions. This, again, poses a question if the conjugate result assures what is claimed in certain controlled trials, holds a consistent strength and direction of effect in extended weeks of gestation. The objective of the present systematic review is to compare the mifepristone plus misoprostol regimen to misoprostol alone in medical abortion of first trimester pregnancy based on randomized or quasi-randomized control trials conducted in different times until December 2021.

Review question(s)
The question/s of this review is: what is the effectiveness, as measured through either risk or odds ratio, of mifepristone plus misoprostol when compared to misoprostol alone for inducing complete expulsion as well as reducing incomplete abortion, missing abortion and ongoing pregnancies when used during first trimester of pregnancy. Furthermore, the review will examine and compare the incidence of potential side effects following administration of the respective regimen in both treatment groups.

Inclusion criteria
Participants
The review will consider studies that included pregnant women with live or dead foetus during the first trimester (≤12 weeks of gestation) and appeared to health facilities for medical abortion. Studies that involved additional means of intervention along with the drugs, included population out of the defined trimester, or those with ectopic pregnancy will be excluded.

Intervention(s)
This review will consider controlled clinical trials with randomized study populations to receive mifepristone plus misoprostol as an intervention group for first trimester abortion. Misoprostol could be administered at least 24 hours apart from mifepristone at any route. When necessary, additional doses of misoprostol might be considered.

Comparator(s)
Populations that have been assigned to receive the misoprostol alone regimen as alternative means of first trimester medical abortion will be considered as comparators. The drug could be administered after or followed by placebo and 3 to 48 hours apart between subsequent doses. Frequency may depend on unit doses and last until at least the third day via any route.

Outcomes
This review will consider incidence of these outcomes: complete expulsion or abortion, incomplete abortion, missed abortion or miscarriage and, ongoing or continuing pregnancy confirmed by ultrasound sonography and an expert’s opinion. In addition, secondary outcomes, such as nausea and vomiting, fever, chills or shivering, subjective report of pain, subjective report of bleeding, diarrhoea, and headache will be evaluated. The outcomes will be reported in either of risk or odds ratio as appropriate.

Types of studies
The review will consider randomized control trials with true, quasi or no-randomization. As the problem in question is best addressed through controlled designs of clinical trials, such studies published from database inception to December 2021 will be included in the review. Because of language barriers, articles published in a language other than English will not be considered.

METHODS
The proposed systematic review will be conducted in accordance with the Joanna Briggs Institute
Search strategy
The search strategy will aim to locate both published and unpublished studies. An initial limited search of Medline and the Cochrane Central will be undertaken to identify articles on the topic. The text words contained in the titles and abstracts of relevant articles, and the index terms used to describe the articles will be used to develop a full search strategy for PubMed/Medline (Appendix I), Cochrane Central (Appendix II), EMBASE (Ovid) (Appendix III), WHO Trial Registration dataset and, google scholar. The search strategy, including all identified keywords and index terms, will be adapted for each included information source. The reference list of all studies selected for critical appraisal will be screened for additional studies.

Information sources
Electronic search of various databases or digital libraries such as PubMed, EMBASE, and the Cochrane CENTRAL will be checked for published reports. Gray literature sources as Google Scholar and the WHO international clinical trial registry platform will be included as source log.

Study selection
Following the search, all identified citations will be collated and uploaded into EndNote and duplicates will be removed. Titles and abstracts will then be screened by two independent reviewers for assessment against the inclusion criteria for the review. Potentially relevant studies will be retrieved in full and their citation details imported into the Joanna Briggs Institute System for the Unified Management, Assessment and Review of Information (JBI SUMARI) (Joanna Briggs Institute, Adelaide, Australia). The full text of selected citations will be assessed in detail against the inclusion criteria by two independent reviewers. Reasons for exclusion of full text studies that do not meet the inclusion criteria will be recorded and reported in the systematic review. Any disagreements that arise between the reviewers at each stage of the study selection process will be resolved through discussion, or with a third reviewer. The results of the search will be reported in full in the final systematic review and presented in a Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram.

ASSESSMENT OF METHODOLOGICAL QUALITY
Eligible studies will be critically appraised by two independent reviewers at the study level for methodological quality in the review using standardized critical appraisal instruments from the Joanna Briggs Institute for experimental studies. Authors of papers will be contacted to request missing or additional data for clarification, when required. Any disagreements that may arise will be resolved through discussion, or with a third reviewer. The results of critical appraisal will be reported in narrative form and in a table.

DATA EXTRACTION
Data will be extracted from studies included in the review by two independent reviewers using the standardized data extraction tool. The data extracted will include specific details about the populations, study methods, interventions, and outcomes of significance to the review objective indicate the specific details. Any disagreements that arise between the reviewers will be resolved through discussion, or with the third reviewer.

DATA SYNTHESIS
Studies will, where possible, be pooled in statistical meta-analysis using review manager (RevMan) software version 5.3. Effect sizes will be expressed as either odds ratios or risk ratio and their 95% confidence intervals will be calculated for analysis. A subgroup analysis will be conducted considering gestational age, dosage and route of administration of misoprostol, or foetal heartbeat status. Heterogeneity will be assessed statistically using the standard chi-squared and I squared tests. Statistical analyses will be performed using either of the fixed or random effect models. A sensitivity analysis will
be conducted by excluding certain studies with relative small effect or exclusion of assumptions for missed data (if available). Likely, robustness of the review will be checked against changes of analysis method. Where statistical pooling is not possible, the findings will be presented in narrative form including tables and figures to aid in data presentation. A funnel plot will be generated using RevMan software to assess publication bias if there are 10 or more studies included in a meta-analysis. Statistical tests for funnel plot asymmetry (Egger test, Begg test, Harbord test) will be performed where appropriate.

ASSESSING CERTAINTY IN THE FINDINGS
The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach for grading the certainty of evidence will be followed and a Summary of Findings (SoF) table will be created using GRADEPro GDT 2015 (McMaster University, ON, Canada). The SoF will present the following information on main outcomes: incidence of complete abortion, missed abortion, incomplete abortion and ongoing pregnancy for the treatment and control groups, estimates of relative risk or odds ratio, and a ranking of the quality of the evidence based on the risk of bias, directness, heterogeneity, precision and risk of publication bias of the review results. Subgroups reports will be included as appropriate.

ACKNOWLEDGEMENTS
The authors of this review acknowledge centre of excellence in reproductive health (COE-RH) of St. Paul’s Hospital Millennium Medical College (SPHMMC) and the Ethiopian evidence based healthcare centre, an affiliate of JBI at Jimma University for arranging a training opportunity on systematic review and meta-analysis.

FUNDING
There is no source of funding for this project.
REFERENCES

1. Costescu D, Guilbert E, Bernardin J, Black A, Dunn S, Fitzsimmons B, et al. Medical Abortion. Journal of obstetrics and gynaecology Canada: JOGC = Journal d'obstetrique et gynecologie du Canada: JOGC. 2016;38(4):366-89.
2. Upadhyay UD, Desai S, Zlidar V, Weitz TA, Grossman D, Anderson P, et al. Incidence of emergency department visits and complications after abortion. Obstetrics and gynecology. 2015;125(1):175-83.
3. Xu W, Zhang W, Zhang X, Dong T, Zeng H, Fan Q. Association between formaldehyde exposure and miscarriage in Chinese women. BioMed research international. 2017;96(26):e7146.
4. Andersen JT, Mastrogiannis D, Andersen NL, Petersen M, Broedbaek K, Cejvanovic V, et al. Diclofenac/misoprostol during early pregnancy and the risk of miscarriage: a Danish nationwide cohort study. Archives of gynecology and obstetrics. 2016;294(2):245-50.
5. Cederbaum JA, Putnam-Hornstein E, Sullivan K, Winetrobe H, Bird M. STD and Abortion Prevalence in Adolescent Mothers With Histories of Childhood Protection Involvement. Perspectives on sexual and reproductive health. 2015;47(4):187-93.
6. Jones HE, O'Connell White K, Norman WV, Guilbert E, Lichtenberg ES, Paul M. First trimester medication abortion practice in the United States and Canada. PloS one. 2017;12(10):e0186487.
7. van den Berg J, Gordon BB, Snijders MP, Vandenbussche FP, Coppus SF. The added value of mifepristone to non-surgical treatment regimens for uterine evacuation in case of early pregnancy failure: a systematic review of the literature. European journal of obstetrics, gynecology, and reproductive biology. 2015;195:18-26.
8. Louie KS, Chong E, Tsereteli T, Avagyan G, Vardanyan S, Winikoff B. The introduction of first trimester medical abortion in Armenia. Reprod Health Matters. 2015;22(44 Suppl 1):56-66.
9. Caldeira-Leite S, Reis DS, de Oliveira KM, Carneiro IM, de Souza JA et al. Efficacy and safety of mifepristone-buccal misoprostol for early medical abortion in an Australian obstetric setting. The Australian & New Zealand journal of obstetrics & gynaecology. 2017;57(3):366-71.
10. Shrestha D, Aryal S, Sharma B. Safety, Efficacy and Acceptability of Early First Trimester Abortion using Oral Mifepristone and Sublingual Misoprostol. Journal of Nepal Health Research Council. 2018;16(3):269-73.
11. Kulier RRK, Gülmezoglu AMM, Hofmeyr GJ, Cheng LLN, Campana A. Medical methods for first trimester abortion. Cochrane Database of Systematic Reviews. 2003, Issue 3. Art. No.: CD002855. DOI: 10.1002/14651858.CD002855.pub2.
12. Kulier R, Kapp N, Gülmezoglu AM, Hofmeyr GJ, Cheng L, Campana A. Medical methods for first trimester abortion. Cochrane Database Syst Rev. 2011 Nov 9;2011(11):CD002855. doi: 10.1002/14651858.CD002855.pub4. PMID: 22071804; PMCID: PMC7144729.
13. Calder A. The clinical use of prostaglandins for early and late abortion. In: Hillier K. (eds) Eicosanoids and Reproduction. Advance in Eicosanoid Research.1987. vol 1. Springer, Dordrecht.
14. Alfirevic Zarko, Keeney Edna, Downwell Therese, Welton Nicky J, Dias Sofia, Jones Leanne V et al. Labour induction with prostaglandins: a systematic review and network meta-analysis BMJ 2015; 350:h217.
15. Mahajan DK, London SN ; Mifepristone (RU486): A review. Fertility and Sterility. 1997. 68 ( 6) Pages 967-976.
16. Schaff EA1, Eisinger SH, Stadilius LS, Franks P, Gore BZ, Poppema S. Low-dose mifepristone 200 mg and vaginal misoprostol for abortion. Contraception. 1999 Jan;59(1):1-6.
17. Ngoc NTN, Shoert C, Raghavan S, Blum J, Nga NTB, Minh NTH, et al. Mifepristone and misoprostol compared with misoprostol alone for second-trimester abortion: a randomized controlled trial. Obstetrics & Gynecology. 2011;118(3):601-8.
18. Kristina Gemzell-Danielsson & Sujata Lalitkumar. Second Trimester Medical Abortion with Mifepristone-Misoprostol and Misoprostol Alone: A Review of Methods and Management, Reproductive Health Matters.2008.16:sup31, 162-172, DOI: 10.1016/S0968-8080(08)31371-8.
19. Hammond C. Recent advances in second-trimester abortion: an evidence-based review. American Journal of Obstetrics & Gynecology. 2009;200(4):347-56.
20. Akkenapally PL. A Comparative Study of Misoprostol Only and Mifepristone Plus Misoprostol in Second Trimester Termination of Pregnancy. J Obstet Gynaecol India. 2016;66(Suppl 1):251–257. doi:10.1007/s13224-016-0869-z
24. Ganatra, Bela et al. Global, regional, and subregional classification of abortions by safety, 2010–14: estimates from a Bayesian hierarchical model. The Lancet, Volume 390, Issue 10110, 2372 - 2381.

25. Singh S et al., Abortion Worldwide 2017: Uneven Progress and Unequal Access, New York: Guttmacher Institute, 2018, pages 1-68.

26. Schreiber CA, Creinin MD, Atrio J, Sonalkar S, Ratcliffe SJ, Barnhart KT. Mifepristone Pretreatment for the Medical Management of Early Pregnancy Loss. The New England journal of medicine. 2018;378(23):2161-70.

27. Chen MJ, Creinin MD. Mifepristone With Buccal Misoprostol for Medical Abortion: A Systematic Review. Obstetrics and gynecology. 2015;126(1):12-21.

28. Kapp N, Baldwin MK, Rodriguez MI. Efficacy of medical abortion prior to 6 gestational weeks: a systematic review. Contraception. 2018;97(2):90-9.

29. Dalenda C, Ines N, Fathia B, Malika A, Bechir Z, Ezzeddine S, et al. Two medical abortion regimens for late first-trimester termination of pregnancy: a prospective randomized trial. Contraception. 2010;81(4):323-7.

30. Chawdhary R, Rana A, Pradhan N. Mifepristone plus vaginal misoprostol vs vaginal misoprostol alone for medical abortion in gestation 63 days or less in Nepalese women: a quasi-randomized controlled trial. Journal of obstetrics and gynaecology research. 2009;35(1):78-85.

31. Tufanaru C, Munn Z, Aromataris E, Campbell J, Hopp L. Chapter 3: Systematic reviews of effectiveness. In: Aromataris E, Munn Z (Editors). Joanna Briggs Institute Reviewer’s Manual. The Joanna Briggs Institute, 2017. Available from https://reviewersmanual.joannabriggs.org/

32. Munn, Z., Aromataris, E., Tufanaru, C., Stern, C., Porritt, K., Farrow, J., Lockwood, C., Stephenson, M., Moola, S., Lizarondo, L. and McArthur, A., 2018. The development of software to support multiple systematic review types: the Joanna Briggs Institute System for the Unified Management, Assessment and Review of Information (JBI SUMARI). International journal of evidence-based healthcare.

33. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097 available at: www.prisma-statement.org.

34. Review Manager (RevMan). Version 5.3. Copenhagen. The Nordic Cochrane Centre, Cochrane Collaboration, 2014.

35. GRADEpro GDT: GRADEpro Guideline Development Tool [Software]. McMaster University, 2015 (Developed by Evidence Prime, Inc.). Available from gradeopro.org.