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REVIEW

Second Trimester Medication Abortion Regimens and the Mifepristone-Misoprostol Dosing Interval

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Abstract

Purpose of Review The purpose of this article is to review current methods of induction termination of pregnancy in the second trimester. The specific area of focus is recent publication regarding timing of mifepristone and misoprostol dosing. Current international guidelines recommend initial treatment with mifepristone followed by misoprostol after 24 to 48 h.

Recent Findings Retrospective studies indicate that a shorter interval between mifepristone and misoprostol of less than 12 h or even concomitant administration may result in a shorter total abortion time without increasing risk of incomplete abortion or complications.

Summary Given the potential benefit of increased efficacy, with successful expulsion of the pregnancy, and reduced time to delivery with shorter mifepristone-misoprostol intervals or concurrent administration practitioners should offer all second trimester medication abortion treatment with mifepristone. Further studies are needed to evaluate the implementation of concurrent or varied dosing intervals and the magnitude of benefit vs risks, with attention to the patient experience, resources, and costs.

Keywords Second trimester abortion · Medical abortion · Induction termination · Mifepristone · Misoprostol · Medication abortion

Introduction

Globally, most abortions are performed in the first trimester with only a small fraction occurring in the second trimester and an even smaller proportion after 20 weeks of gestation. Factors that contribute to the need for later trimester termination include decisional conflict, delayed recognition of pregnancy, limited access to abortion services, new onset or worsening of maternal medical conditions, and delay in fetal diagnosis. Abortion during the second trimester may be performed either medically or surgically. Induction termination is a critical medical treatment and an important alternative to surgical dilation and evacuation, especially in areas with few providers trained in surgical abortion [1]. Appropriate patients should be counseled regarding options and offered termination induction or medication abortion in the second trimester as a safe and effective form of termination. For the purpose of this this review, the second trimester is defined as 12 to 28 weeks in order to encompass the range of recommendations referenced.

Induction termination offers several unique characteristics such as an opportunity to participate in labor, option for the pregnant person and their family time to grieve with and/or hold the fetus if desired, improves tissue integrity for autopsy evaluation, and possible avoidance of a procedure in the operating room. Approximately 3–7% of medication abortions after 14 weeks estimated gestational age (EGA) are unsuccessful. The average induction time for misoprostol only regimens in the second trimester is approximately 18 h (typically 5 doses of misoprostol). Up to 20% of medication abortions in the second trimester may require uterine aspiration for retained products of conception. Complications are rare and are comparable to the rates observed for persons undergoing surgical procedures. Complications include infection requiring antibiotics (1%) or hemorrhage requiring transfusion (1%) [1].

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Retrospective reviews and prospective clinical trials have demonstrated that misoprostol regimens are superior to other agents (i.e., hypertonic saline, gemprost, or oxytocin) used to induce labor [2, 3]. Additionally, higher doses of vaginally administered misoprostol, such as 2400 µg over 24 h, with regular dosing intervals every 3–4 h, are superior to lower misoprostol doses, orally ingested dosing, or longer dosing intervals (such as every 6 h) in effectively completing the abortion (Table 1). The RCOG endorses 800 µg of misoprostol followed by 400 µg every 3 h [4]. The World Health Organization recommends misoprostol 400 µg every 3 h [5]. Misoprostol side effects include nausea, vomiting, diarrhea, and pyrexia/fever, all of which are more common with oral ingestion dosing when compared to vaginal [2].

The concurrent use of cervical dilators, such as laminaria tent dilators or an inflated cervical foley balloon, have not demonstrated improved efficacy in terms of delivery of the pregnancy, induction interval, or improved safety profile compared to mifepristone and misoprostol medication regimens [6]. Administration of dilute oxytocin and redosing of misoprostol after delivery of the fetus have been reported hasten delivery of the placenta [7]. Delivery intervals of 2–4 h between fetus and placenta have been reported without increase in associated morbidity for hemodynamically and medically stable persons [8]. Feticide may be indicated depending on the institutional practices, patient and provider preferences, and/or legal landscape. It is important to prepare care-givers, support persons, and the patient regarding professional standards and norms regarding how signs of life from the pregnancy are clinically managed and legally documented for a non-viable or peri-viable fetus or pregnancy. For these reasons, some settings may offer or recommend feticidal procedures at a certain gestational age or based on patient desires (Fig. 1). Risk of uterine rupture is a rare complication that may be more prevalent among persons with prior uterine rupture, prior uterine surgery, and grand-multiparity [9]. However, uterine rupture has been observed in women without risk factors for uterine rupture. Existing data regarding this risk are limited by small sample size and variability in regimen. Two or more prior low transverse cesarean section surgeries, other hysterotomies, and increasing estimated gestational age (greater than 29 weeks) can all be reasons to consider a lower dose of misoprostol, a longer dosing interval or alternative methods such as cervical foley balloon dilation or dilute infusion of oxytocin administration [11].

Studies over the past several decades have definitively demonstrated regimens that includes the progesterone antagonist, mifepristone, along with misoprostol are superior to the use of misoprostol alone [12, 13, 10]. Mifepristone in advance of misoprostol can reduce induction interval from initiation of misoprostol to delivery of fetus: from 10–24 h to less than 7 h. This reduction in time spent on a monitored or higher acuity setting mitigates cost and is a favorable outcome for patients. Current national and international guidelines recommend a 24-to-48-h interval between mifepristone pretreatment and first dosage of misoprostol for induction termination in both the second and third trimester [5]. However, a shorter dosing interval with either same-day or concurrent dosing offers potential benefits to certain patients, clinicians, and health care systems in depending on the context. An abbreviated dosing interval may decrease the total abortion time and reduce the number of clinic or hospital encounters, which are costs and burdens on the care team and most importantly to the patient.

We are incorporating publications that present compelling evidence for the benefit of abbreviated dosing intervals less than 24 h or concurrent mifepristone administration with the initiation of misoprostol. A shortened dosing interval could offer important advantages for some patient presentations, cultural context, or specific resource care settings. While the studies discussed in the following review focus primarily on the second trimester, some publications suggest that these findings may be extrapolated beyond to the third trimester such as in the case of IUFD or late diagnosis of severe anomalies [12, 14]. Mifepristone should be considered as pretreatment for medication abortion at all gestational ages and at any dosing interval, including concurrent administration based on the findings of the following publications.

Timing of Mifepristone/Misoprostol Dosing

In 2020, Henkel et al. [15••] published a study evaluating the effect of shorter interval between mifepristone and misoprostol dosing in second trimester medical abortions via retrospective study design. The study period was conducted over a 10-year interval and evaluated patients undergoing a medical termination using mifepristone and misoprostol

Table 1 Misoprostol dosing regimen for medication abortion

EGA	Misoprostol dose
< 24 w 6 d	800 mcg per vagina × 1 then 400 mcg vaginal or buccal every 3 h
25 w 0 d–28 w 6 d	600 mcg per vagina × 1 then 200 mcg vaginal or buccal every 3 h
≥ 29 w	100 mcg per vagina × 1 then 50 mcg vaginal or buccal every 3 h

EGA estimated gestational age

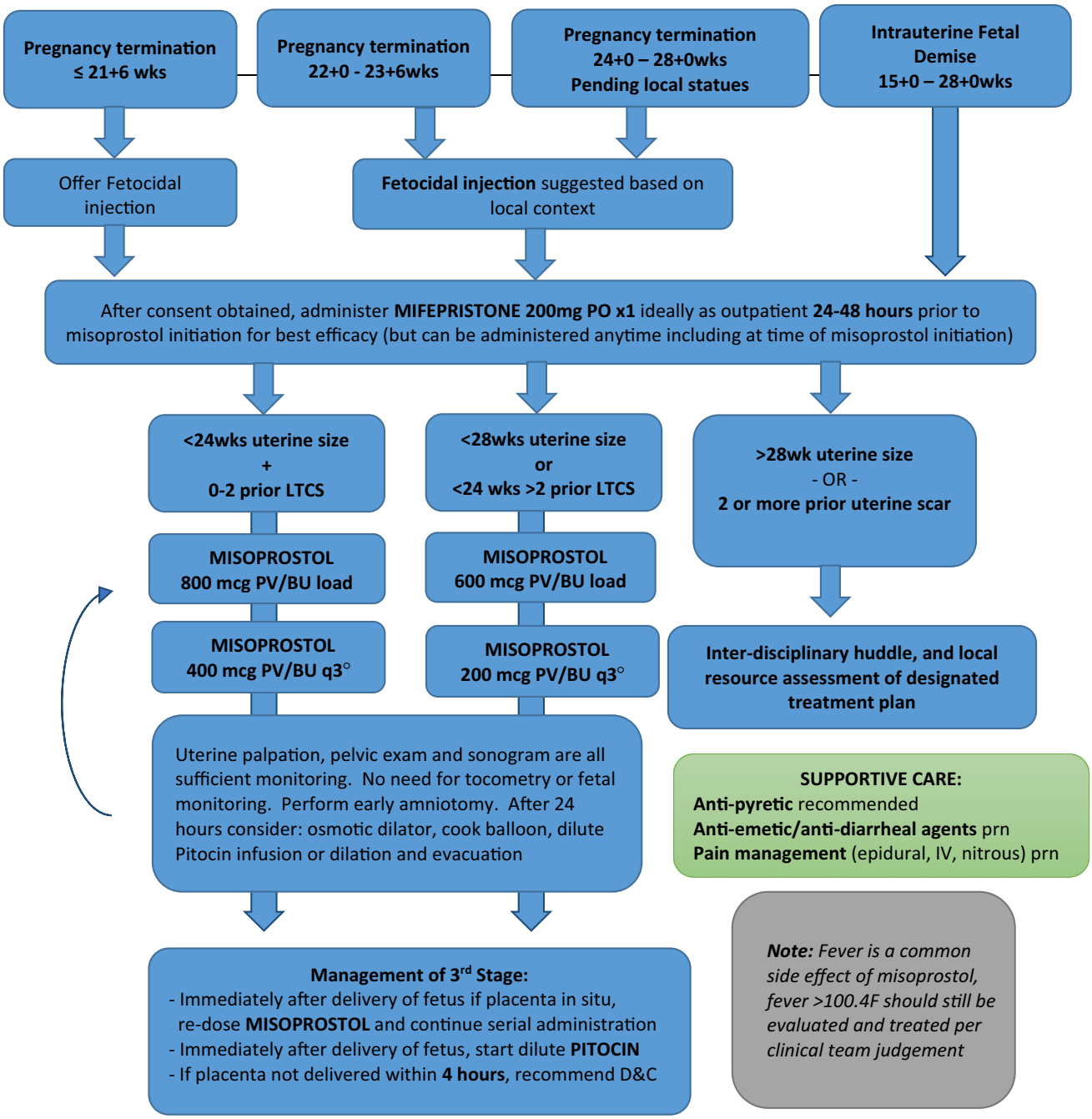

Fig. 1 Medication abortion induction of labor 15–28 weeks' sample flowchart

between 15 and 27 weeks gestation. Patients with intrauterine fetal demise, rupture of membranes, cervical insufficiency, preeclampsia, or concomitant placement of osmotic dilators were excluded. Patients ingested 200 mg mifepristone followed by 400 mcg misoprostol buccally every 3 h while admitted to the hospital until expulsion of the fetus. The medical record was reviewed, and the following data extracted: interval of mifepristone to misoprostol administration, time to fetal expulsion, demographic characteristics, feticidal procedures, and occurrence of complication. The primary outcome was total abortion time (defined as mifepristone to fetal expulsion) and total induction time (first dose of misoprostol to expulsion).

During the 10-year study period, 140 patients were identified of whom 89 were included in the final data set. The median gestational age was 22 weeks (range 15 to 27 weeks) with average parity of one. No significant differences were noted between the groups as classified by mifepristone

misoprostol dosing interval. The dosing intervals examined were less than 12 h, 12–24 h, and greater than 24 h. The median times observed for each of these groups were 8.8 h, 17.7 h, and 30.5 h, respectively. The median total abortion time differed between groups with statistical significance however the median induction time was similar. A linear trend was noted that as mifepristone-misoprostol dosing interval increases, the induction time decreased but the total abortion time increased. The proportion of persons with completed abortion inductions was similar across all treatment groups. Complications were observed in 27 (30.3%) of all cases distributed across all treatment intervals. Authors noted that persons with a 12–24-h mifepristone-misoprostol interval were more likely to undergo curettage for retained placenta, but the study was not powered or designed to detect this difference.

In 2021, Shay and colleagues [16••] evaluated same day administration of mifepristone with misoprostol in second trimester terminations. Persons between 14 and 28 weeks of gestation were identified between 2009 and 2018, and those undergoing induction for any indication, including intrauterine fetal demise and preterm prelabor rupture of membranes, were included. Persons who had cervical preparation with osmotic dilators were also included. The primary outcome was defined as a proportion of persons who experienced expulsion of the fetus within 24 h from the initial dose of misoprostol. Secondary outcomes included expulsion within 12 h, need for subsequent instrumentation (either D&C or D&E), use of oxytocin, estimated blood loss, and length of hospitalization.

During this period, 325 potential cases were identified of whom 298 were included in the analysis. Of these, 94 received misoprostol on the same calendar day as mifepristone with a mean interval of 1.22 h (range 0 to 11.3 h). The remaining 204 persons did not receive mifepristone. Baseline characteristics of the two groups were similar with a median age of 30 years and a mean gestational age of 21.5 weeks. Most pregnancies (65%) had a diagnosis of a fetal anomaly. Among 95% of patients, misoprostol was administered vaginally. Persons in the mifepristone-misoprostol group received 400 mcg misoprostol every 3 h; persons in the misoprostol-only group received 600 mcg every 4 h. The proportion of patients with concurrent use of osmotic dilators differed between the two groups with 1.1% in the mifepristone-misoprostol and 40.2% in the misoprostol only groups, respectively.

The primary outcome, defined as expulsion within 24 h from first misoprostol dose, occurred in 93% of the mifepristone-misoprostol patients and in 79.9% of the misoprostol only group with a risk ratio of 1.17 (95% CI 1.07–1.28). Expulsion within 12 h occurred in 56.4% of the mifepristone-misoprostol group and in 34.0% of the misoprostol. The median time to expulsion was 689 and 901 min across the two treatment groups. There were no differences between the groups in retained products of conception, use of oxytocin, total dose of misoprostol, or estimated blood loss. Subgroup analysis suggests that those within intrauterine fetal demise experienced higher rates of expulsion within 24 h, lower median total dose of misoprostol, and higher rates of retained products of conception compared to those who received feticidal treatment.

These studies add to the growing body of evidence that suggest that an interval of less than 48 h as well as an interval far less than 24 h for mifepristone-misoprostol dosing is associated with a clinically significant decrease in the total abortion time without a change the risk profile or possible total induction time in the second trimester. Adopting a modified dosing schedule with either a significantly shortened interval or concurrent administration of the two agents will likely improve the patient experience.

Collectively, these studies are limited by their retrospective nature and relatively small sample sizes, which may be underpowered to detect differences in rarer complications. Additionally, direct comparison of the studies is limited by the choice of exclusion criteria, primary outcomes measured, misoprostol dosing regimens, and use of osmotic dilators.

Medication induction abortion research would be substantially elevated by consistent and widely endorsed standardized outcomes similar to those set forth for abortion research in 2021 [17] "Standardized outcomes in abortion research could decrease heterogeneity among trials and improve the quality of systematic reviews and clinical guidelines. Researchers should select, collect, and report these core outcomes in future abortion trials. Journal editors should advocate for core outcome set reporting."

Conclusion

Mifepristone clearly increases the effectiveness and safety of induction abortion when given 24 to 48 h prior to administration of misoprostol [5] in the second trimester. Based on limited studies, these data are likely generalizable to more advanced gestational ages. The use and timing of mifepristone can likely be extrapolated to uses in the third trimester; however, clinical studies of this context are limited. Forthcoming studies provide evidence for the effectiveness of shorter interval dosing with either same day or concurrent administration in the second trimester. Decreasing the interval of administration appears to reduce the total abortion time without significantly increasing the rate of complication or need for additional surgical procedures such as uterine aspiration. Where mifepristone is available, should be strongly considered for administration on the same day as induction if advance administration is not possible.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
•• Of major importance

1. Cohen MA, Kapp N, Edelman A. Abortion care beyond 13 weeks' gestation: a global perspective. Clin Obstet Gynecol. 2021;64(3):460–74.
2. Dodd JM, Crowther CA. Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death. Cochrane Database of Syst Rev 2010;4:CD004901. https://doi.org/10.1002/14651858.CD004901.pub2. Accessed 07 December 2022.
3. Abediasl Z, Sheikh M, Pooransari P, Farahani Z, Kalani F. Vaginal misoprostol versus intravenous oxytocin for the management of second-trimester pregnancies with intrauterine fetal death: a randomized clinical trial. J Obstet Gynaecol Res. 2016;42(3):246–51.
4. The Care of Women Requesting Induced Abortion (Evidence-based Clinical Guideline No. 7). Royal College of Obstetricians & Gynaecologists (RCOG). November 2011, reaffirmed 2018.
5. Abortion care guideline. Geneva: World Health Organization (WHO); 2022. License: CC BY-NC-SA 3.0 IGO.
6. Anselem O, Jouannic JM, Winer N, Bouchghoul H, Vivanti AJ, Quibel T, Massardier J, Rousseau J, Ancel PY, Goffinet F, Tsatsaris V. Cervical dilators used concurrently with misoprostol to shorten labor in second-trimester termination of pregnancy: a randomized controlled trial. Obstet Gynecol. 2022 Sep 1;140(3):453–460. https://doi.org/10.1097/AOG.0000000000004887. Epub 2022 Aug 3. Erratum in: Obstet Gynecol. 2022;140(5):902. PMID:35,926,202.
7. Dickinson JE, Evans SF. A comparison of oral misoprostol with vaginal misoprostol administration in second-trimester pregnancy termination for fetal abnormality. Obstet Gynecol. 2003;101(6):1294–9.
8. Green J, Borgatta L, Sia M, Kapp N, Saia K, Carr-Ellis S, Vragovic O. Interventions rates for placental removal following induction abortion with misoprostol. Contraception. 2007;76(4):310–3.
9. Berghella V, Airoldi J, O'Neill AM, Einhorn K, Hoffman M. Misoprostol for second trimester pregnancy termination in women with prior cesarean: a systematic review. BJOG. 2009;116:1151–7.
10. Borgatta L, Kapp N. Society of Family Planning. Clinical guidelines. Labor induction abortion in the second trimester Contraception. 2011;84(1):4–18. https://doi.org/10.1016/j.contraception.2011.02.005. Epub 2011 Mar 30. PMID:21664506.
11. Perritt JB, Burke A, Edelman AB. Interruption of nonviable pregnancies of 24–28 weeks' gestation using medical methods: release date June 2013 SFP guideline #20,133. Contraception. 2013;88(3):341–9.
12. Vlad S, Boucoiran I, St-Pierre ÉR, Ferreira E. Mifepristone-misoprostol use for second- and third-trimester medical termination of pregnancy in a Canadian tertiary care centre. J Obstet Gynaecol Can. 2022;44(6):683–689. https://doi.org/10.1016/j.jogc.2021.12.010. Epub 2022 Feb 1. PMID:35,114,381.
13. Wildschut H, Both MI, Medema S, Thomee E, Wildhagen MF, Kapp N. Medical methods for mid-trimester termination of pregnancy. Cochrane Database Syst Rev. 2011;2011(1):CD005216. https://doi.org/10.1002/14651858.CD005216.pub2. PMID:21,249,669; PMCID:PMC8557267.
14. Prodan N, Breisch J, Hoopmann M, Abele H, Wagner P, Kagan KO. Dosing interval between mifepristone and misoprostol in second and third trimester termination. Arch Gynecol Obstet. 2019;299(3):675–679. https://doi.org/10.1007/s00404-018-5017-9. Epub 2018 Dec 21. PMID:30,578,439
15. •• Henkel A, Lerma K, Blumenthal PD, Shaw KA. Evaluation of shorter mifepristone to misoprostol intervals for second trimester medical abortion: a retrospective cohort study. Contraception. 2020 Nov;102(5):327–331. https://doi.org/10.1016/j.contraception.2020.06.009. Epub 2020 Jun 25. PMID:32,592,800. **A retrospective review of 89 persons with gestations 15–27 weeks who received misoprostol and mifepristone at different dosing intervals (less than 12 h, 12–24 h, and greater than 24 h) and a subsequent analysis of total induction time as well as total abortion time.**
16. •• Shay RL, Benson LS, Lokken EM, Micks EA. Same-day mifepristone prior to second-trimester induction termination with misoprostol: a retrospective cohort study. Contraception. 2022;107:29–35. https://doi.org/10.1016/j.contraception.2021.09.006. Epub 2021 Sep 13. PMID:34,529,952. **A retrospective review of 298 persons with gestations 14–28 weeks who received misoprostol and mifepristone at varying intervals and an analysis of time to fetal expulsion.**
17. Allanson ER, Copson S, Spilsbury K, et al. Pretreatment with mifepristone compared with misoprostol alone for delivery after fetal death between 14 and 28 weeks of gestation: a randomized controlled trial. Obstet Gynecol. 2021;137(5):801–9. https://doi.org/10.1097/AOG.0000000000004344.
18. Dadhwal V, Garimella S, Khoiwal K, Sharma KA, Perumal V, Deka D. Mifepristone followed by misoprostol or ethacridine lactate and oxytocin for second trimester abortion: a randomized trial. Eurasian J Med. 2019;51(3):262–266. https://doi.org/10.5152/eurasianjmed.2019.18341. Epub 2019 Aug 19. PMID:31,692,613; PMCID:PMC6812907.
19. Whitehouse KC, Stifani BM, Duffy JMN, Kim CR, Creinin MD, DePiñeres T, Winikoff B, Gemzell-Danielsson K, Blum J, Sherman RB, Lavelanet AF, Brahmi D, Grossman D, Tamang Gebreselassie H, Ponce de Leon RG, Ganatra B. Standardizing abortion research outcomes (STAR): results from an international consensus development study. Contraception. 2021 Nov;104(5):484–491. https://doi.org/10.1016/j.contraception.2021.07.004. Epub 2021 Jul 14. PMID:34,273,335; PMCID:PMC8609158.
20. National Guideline Alliance (UK). Medical abortion after 24 weeks' gestation: abortion care: evidence review L. London: National Institute for Health and Care Excellence (NICE); 2019 Sep. PMID:32,813,471.
21. Valero I, Garcia-Jimenez R, Weber-Fernandez AM, et al. Combination of mifepristone and misoprostol vs misoprostol monotherapy for treatment of second-trimester pregnancy loss. Eur J Contracept Reprod Health Care. 2022;27(4):341–4. https://doi.org/10.1080/13625187.2022.2054982.

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