Adv Ther (2019) 36:1246–1251
https://doi.org/10.1007/s12325-019-00953-2

REVIEW

Adjunctive Agents for Cervical Preparation in Second Trimester Surgical Abortion

Jessika A. Ralph · Lee P. Shulman

Received: January 31, 2019 / Published online: April 19, 2019

ABSTRACT

Late second trimester dilation and evacuation is a challenging subset of surgical abortion. Among the reasons for this is the degree of cervical dilation required to safely extricate fetal parts. Cervical dilation is traditionally achieved by placing multiple sets of osmotic dilators over two or more days prior to the evacuation procedure; however, there is interest in shortening cervical preparation time. The use of adjuvant mifepristone and misoprostol in conjunction with osmotic dilators has been studied for this purpose, and their use demonstrates that adequate cervical dilation can be achieved in less time than with dilators alone. We present a review of the current evidence surrounding adjunctive agents for cervical preparation, and contend that for women presenting for surgical abortion care above 19 weeks gestation, the use of adjunctive mifepristone and/or misoprostol should be strongly considered along with osmotic dilator insertion when cervical preparation in less than 24 h is needed.

Keywords: Cervical preparation; Dilation and evacuation; Induced abortion; Mifepristone; Misoprostol

Enhanced Digital Features To view enhanced digital features for this article go to https://doi.org/10.6084/m9.figshare.7946399.

J. A. Ralph · L. P. Shulman (✉)
Section of Family Planning, Department of Obstetrics and Gynecology, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA
e-mail: lee.shulman@nm.org

L. P. Shulman
Division of Clinical Genetics, Department of Obstetrics and Gynecology, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA

INTRODUCTION

Approximately 10% of surgical abortions in the USA occur in the second trimester, and 10% of those occur after 20 weeks gestation. This small subset of abortions is often the result of fetal or maternal pregnancy complications, which can be emotionally challenging; patients value the ability to discuss all management options, including both medical and surgical pregnancy termination, with their provider [1]. Most of these abortions will be accomplished surgically by dilation and evacuation (D&E), a safe and efficient method of pregnancy termination [2]. As gestational age advances, the amount of dilation required for safe and facile removal of fetal parts increases, increasing the risk of cervical laceration. Preparation of the cervix prior to the evacuation procedure decreases this risk to less than 1% of cases [3].

Cervical preparation for adequate dilation can be achieved by pharmacological regimens, mechanical processes, or both. Pharmacologic preparation involves administration of either mifepristone, misoprostol, or both prior to the procedure. Misoprostol is a prostaglandin E_1 analogue that induces uterine contractions and is widely used alone for cervical preparation in late first and early second trimester abortion as it decreases the risk of cervical injury [4–7]. Mifepristone is an antiprogestin which causes cervical softening and increases sensitivity to prostaglandins [8, 9]. It has been extensively studied for its use in first trimester medical abortion, third trimester labor induction, and more recently as an agent for cervical preparation in the second trimester. Mechanical dilation involves placement of osmotic dilators into the cervix. The two most common dilator types are laminaria and the synthetic Dilapan-S. Laminaria are derived from dehydrated seaweed stems of *Laminaria japonica* and *Laminaria digitata*; Dilapan-S comprises a polyacrylate-based hydrogel. Both laminaria and Dilapan-S absorb cervical fluid to swell to 3–4 times their original diameter, causing cervical dilation by radial force. Laminaria also induce prostaglandin synthesis, prompting cervical softening in addition to mechanical force [10].

Late second trimester D&E represents a challenging subset of surgical abortions because of the amount of cervical dilation required to extricate fetal parts in a safe and facile manner, as well as to obtain appropriate tissue for analysis in cases characterized by certain fetal anomalies [11]. Cervical dilation for these procedures has been traditionally accomplished by placing multiple sets of dilators over multiple days prior to surgical evacuation. However, a multi-visit several day abortion encounter is not feasible in many settings for either the patient or the provider. Because of the need to reduce the number of provider visits, there has been considerable interest in the use of adjuvant pharmacologic therapy to hasten cervical preparation. Misoprostol was initially used in this context and has been studied and evaluated as an adjuvant dilating agent. More recently, mifepristone has begun to be used for adjuvant cervical preparation. We will review here the clinical data for these adjuvant dilation agents.

METHODS

One author, JAR, performed the literature search. PUBMED was searched for English-language articles from 1966 through March 2018 using the following keywords: mifepristone, misoprostol, second trimester abortion, second trimester termination, dilation and evacuation, dilator, laminaria. Both review and original research articles were included in the literature assessment. References of all reviewed articles were also searched for additional topically relevant articles. The authors then reviewed and summarized the articles prior to preparation of the narrative review. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Adjuvant Misoprostol

While we aim to review the use of adjuvant pharmacology for cervical preparation, it should be noted that osmotic dilators can be successfully used alone. One of the largest case series examining the use of laminaria to date, comprising over 11,000 D&Es, was put together by Peterson et al. This work continues to be cited as a compelling argument for the use of laminaria to prevent cervical laceration in second trimester surgical abortion, which was reduced from 8% in women over 20 weeks to 1.4%. The risk of an incomplete procedure, regardless of whether laminaria were used, was rare [3]. However, there remain instances where adjuvant pharmacology could improve cervical preparation; the discussion of these instances follows.

Misoprostol has been shown to be an effective cervical priming agent in the first trimester, producing preoperative cervical dilation comparable to laminaria in late first trimester surgical abortions [12]. The use of misoprostol in this setting has been shown to reduce the total abortion time to 1 day, compared with 2 days when laminaria are used [7]. Several researchers

have used these data to inform their use of adjunctive misoprostol for second trimester D&E.

Two studies have examined the use of misoprostol in the setting of overnight osmotic dilators. Edelman et al. performed a randomized, double-blinded, placebo-controlled trial to assess whether the addition of misoprostol to overnight laminaria produced superior cervical dilation compared to placebo in women between 13 and 20 6/7 weeks gestation. They demonstrated that in participants over 19 weeks gestation, greater dilation (53.6 mm vs 48.5 mm, $p = 0.01$) was achieved when misoprostol was administered adjunctively. Surgeons also found dilation easier to accomplish when participants over 16 weeks gestation received adjunctive misoprostol. There was no difference reported in procedural complications. Conversely, participants in the adjunctive misoprostol group did experience more pain than those receiving placebo [13]. Drey et al. performed a similar trial of late second trimester D&E procedures comparing adjunctive misoprostol to placebo in women receiving overnight osmotic dilators between 21 and 23 6/7 weeks. The benefit of misoprostol was more modest in this gestational age cohort: procedural time was reduced by 1.7 min ($p = 0.02$), and cervical dilation was 2 mm greater ($p = 0.04$). Though not statistically significant, the group that received misoprostol had more instances of cervical laceration than the placebo group (13% vs 6%, $p = 0.09$) [14], raising concern that the cervical softening produced by misoprostol, while likely contributing to easier dilation, was also potentially a risk factor for cervical injury. However, Patel et al. performed a retrospective, descriptive study regarding the use of misoprostol for cervical preparation in 2005, including more than 2200 D&E cases from 12 to 23 6/7 weeks gestation. Though the review included patients that received misoprostol alone for cervical preparation in addition to those receiving it adjunctively with laminaria, the rate of cervical laceration was 5.4 per 1000 and the overall adverse event rate was also low (19.39 events per 1000). Their review strongly suggests that women receiving misoprostol for cervical preparation in the second trimester are not at increased risk of adverse events [15].

Two additional studies review the possibility of same day cervical preparation in second trimester D&E. Lyus et al. performed a retrospective chart review of patients between 18 and 21 6/7 weeks receiving same-day Dilapan-S and adjunctive misoprostol for cervical preparation. The overall complication rate was 1.8% in a review of 274 patients, comparable to similar published rates using overnight cervical preparation regimens. It is important to note that patient selection by providers may have biased the results by choosing only those participants at lowest risk of abortion complications at baseline, as evidenced by the low rate of women with prior cesarean ($\sim$ 7%) [16]. Boraas et al. followed with a randomized trial of adjunctive misoprostol in women between 16 and 20 6/7 weeks receiving same-day cervical preparation with Dilapan-S. With regard to the primary outcome of procedure time, no difference was found between the misoprostol and placebo group (11.1 vs 13.5 min, $p = 0.17$); however, the study was closed prematurely because of two severe adverse events in the placebo group and was therefore underpowered. Importantly, women greater than 19 weeks and women who received Dilapan-S alone were at increased risk of cervical laceration [17]. Though an underpowered study, the adverse events that occurred contend for use of adjuvant misoprostol for same-day D&E, along with careful consideration of the appropriateness of candidates over 19 weeks.

The optimal dose, time interval, and route of misoprostol for adjuvant use have not been determined, and administration varied among the above studies. The most frequently used dose is 400 μg [12, 13, 16], inferred from dosage studies in first trimester surgical abortion which demonstrated that dosages above 400 μg increased side effects without improving cervical dilation [18]. Buccal administration is often chosen in studies of adjunctive cervical preparation [12–14, 16], as it is unknown whether vaginal administration is affected by the presence of dilators and/or sponges; however, the large series by Lyus et al. demonstrates efficacy with vaginal administration [16]. Time interval

is often informed by studies of vaginally administered misoprostol, demonstrating that peak effect occurs between 3 and 4 h after administration [19], but shorter time intervals have been shown to be efficacious [20].

Adjuvant Mifepristone

Mifepristone is known to improve time to delivery in second trimester induction abortion [21]. Several investigators have hypothesized whether similar cervical priming effects take place prior to second trimester surgical abortion. Goldberg et al. performed a three-armed randomized controlled trial comparing the addition of adjunctive mifepristone vs adjunctive misoprostol vs overnight osmotic dilators alone in women between 16 and 23 6/7 weeks. No difference was found between arms for operative time (primary outcome), defined as the time from the first instrument placed into the uterus to the last instrument removed from the uterus. However, procedural time, defined as speculum placement to speculum removal, was shorter when mifepristone was used (9.42 vs 10.35 vs 13.39 min, $p = 0.007$) in participants over 19 weeks. Surgeons also rated procedures in the mifepristone group as easiest. Participants that received mifepristone did not have additional side effects on top of those attributable to the dilators, and acute complications were not statistically different among the three groups [22].

Shaw et al. performed a randomized trial of participants between 19 and 23 6/7 weeks receiving either 2 days of osmotic dilators and adjunctive misoprostol to 1 day of osmotic dilators with adjunctive misoprostol and mifepristone. Operative time was equivalent between groups (11 min 52 s vs 10 min 56 s, $p = 0.72$), supporting the practice that mifepristone allows cervical preparation to safely be reduced to 1 day in the late second trimester [23]. The same group performed a follow-up study in 2017 with three arms: mifepristone, dilators, and misoprostol; placebo, dilators, and misoprostol; mifepristone and misoprostol alone. Adjunctive mifepristone and misoprostol trended towards a shorter procedure time compared to adjunctive misoprostol alone in the most advanced gestational age cohort, but was not statistically significant (10 vs 13 min, $p = 0.42$). More importantly, elimination of osmotic dilators led to more cervical lacerations, demonstrating their continued importance for safe cervical dilation in late second trimester D&E procedures [24].

Dosage and timing of mifepristone are inferred from its use in the context of medical abortion, where 200 mg is administered orally 24–36 h prior to use of prostaglandin to induce uterine contractions [25]. The time interval is informed by human studies that showed an increase in uterine contractility 24–36 h after administration of mifepristone [26]. While studies in first trimester medical abortion have demonstrated efficacy when this time interval is reduced [27], this has not yet been studied in the setting of cervical preparation for second trimester surgical abortion.

CONCLUSIONS

Cervical dilation in second trimester surgical abortion is a critical component in performing safe uterine evacuation procedures. While there are pharmacological agents and mechanical processes appropriate for use in such cases, published data thus far support the use of adjuvant pharmacotherapy in patients beyond 19 weeks in settings where only 1 day of cervical preparation is planned. In same-day settings, adjuvant misoprostol should be used in patients above 16 weeks; there is no published evidence for mifepristone in this setting, but the agent's long time-to-onset would likely make its benefit negligible [28, 29].

Our review also highlights the considerable gaps in the current literature. Only one study has attempted to elucidate mifepristone's benefit without misoprostol in conjunction with osmotic dilator use. Understanding the additive role of mifepristone will be helpful in settings where its relative cost compared to misoprostol is prohibitive. Alternatively, mifepristone is generally well-tolerated, while misoprostol generally adds to pre-procedural discomfort [14, 17]. Therefore, if mifepristone were to be

shown to have benefit in comparison to misoprostol, patients and clinicians would certainly prefer its use. In addition, the best route for misoprostol delivery has not yet been established, with most studies employing buccal administration because of concern for proper placement when laminaria are present. Optimal timing of mifepristone and misoprostol, both together and independently, have also not yet been established. Many of the limitations recognized in our review are related to the use of proxies for adverse events, exemplified by outcome data such as procedure time or cervical dilation. As such, these proxies for adverse outcomes contribute to the heterogeneity of outcomes described above and currently limit ours and others ability to determine which regimen, or combination thereof, provides for the best clinical outcome. In this regard, performing larger trials could better establish which cervical preparations provide for best clinical outcomes in surgical abortions.

This review of adjuvant pharmacologic agents demonstrates that providers employ multiple methods of cervical preparation tailored to the patient, her pregnancy, and the abortion setting. This review supports such an individualized approach for cervical preparation in second trimester abortion procedures.

ACKNOWLEDGEMENTS

Funding. No funding or sponsorship was received for this study or publication of this article.

Authorship. All named authors meet the International Committee of Medical Journal Editors criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosures. Jessika Ralph and Lee Shulman have nothing to disclose.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

REFERENCES

1. Kerns J, Vanjani R, Freedman L, Meckstroth K, Drey EA, Steinauer J. Women's decision making regarding choice of second trimester termination method for pregnancy complications. Int J Gynaecol Obstet. 2012;116(3):244–8.

2. Thorp JM Jr. Public health impact of legal termination of pregnancy in the US: 40 years later. Scientifica (Cairo). 2012;2012:980812.

3. Peterson WF, Berry FN, Grace MR, Gulbranson CL. Second-trimester abortion by dilatation and evacuation: an analysis of 11,747 cases. Obstet Gynecol. 1983;62(2):185–90.

4. Ngai SW, Chan YM, Tang OS, Ho PC. The use of misoprostol for pre-operative cervical dilatation prior to vacuum aspiration: a randomized trial. Hum Reprod. 1999;14(8):2139–42.

5. Nucatola D, Roth N, Saulsberry V, Gatter M. Serious adverse events associated with the use of misoprostol alone for cervical preparation prior to early second trimester surgical abortion (12–16 weeks). Contraception. 2008;78(3):245–8.

6. MacIsaac L, Grossman D, Balistreri E, Darney P. A randomized controlled trial of laminaria, oral misoprostol, and vaginal misoprostol before abortion. Obstet Gynecol. 1999;93(5 Pt 1):766–70.

7. Allen RH, Goldberg AB. Cervical dilation before first-trimester surgical abortion (< 14 weeks' gestation). Contraception. 2016;93:277–91.

8. Clark K, Ji H, Feltovich H, Janowski J, Carroll C, Chien EK. Mifepristone-induced cervical ripening: structural, biomechanical, and molecular events. Am J Obstet Gynecol. 2006;194(5):1391–8.

9. Gemzell-Danielsson K, Bygdeman M, Aronsson A. Studies on uterine contractility following mifepristone and various routes of misoprostol. Contraception. 2006;74(1):31–5.

10. Hayes JL, Fox MC. Cervical dilation in second-trimester abortion. Clin Obstet Gynecol. 2009;52(2):171–8.

11. Shulman LP, Ling FW, Meyers CM, Shanklin DR, Simpson JL, Elias S. Dilation and evacuation for second-trimester genetic pregnancy termination. Obstet Gynecol. 1990;75(6):1037–40.

12. Burnett MA, Corbett CA, Gertenstein RJ. A randomized trial of laminaria tents versus vaginal misoprostol for cervical ripening in first trimester surgical abortion. J Obstet Gynaecol Can. 2005;27(1):38–42.

13. Edelman AB, Buckmaster JG, Goetsch MF, Nichols MD, Jensen JT. Cervical preparation using laminaria with adjunctive buccal misoprostol before second-trimester dilation and evacuation procedures: a randomized clinical trial. Am J Obstet Gynecol. 2006;194(2):425–30.

14. Drey EA, Benson LS, Sokoloff A, Steinauer JE, Roy G, Jackson RA. Buccal misoprostol plus laminaria for cervical preparation before dilation and evacuation at 21–23 weeks of gestation: a randomized controlled trial. Contraception. 2014;89(4):307–13.

15. Patel A, Talmont E, Morfesis J, et al. Adequacy and safety of buccal misoprostol for cervical preparation prior to termination of second-trimester pregnancy. Contraception. 2006;73(4):420–30.

16. Lyus R, Lohr PA, Taylor J, Morroni C. Outcomes with same-day cervical preparation with Dilapan-S osmotic dilators and vaginal misoprostol before dilatation and evacuation at 18 to 21+ 6 weeks' gestation. Contraception. 2013;87(1):71–5.

17. Boraas CM, Achilles SL, Cremer ML, Chappell CA, Lim SE, Chen BA. Synthetic osmotic dilators with adjunctive misoprostol for same-day dilation and evacuation: a randomized controlled trial. Contraception. 2016;94(5):467–72.

18. Singh K, Fong YF, Prasad RN, Dong F. Randomized trial to determine optimal dose of vaginal misoprostol for preabortion cervical priming. Obstet Gynecol. 1998;92(5):795–8.

19. Singh K, Fong YF, Prasad RN, Dong F. Evacuation interval after vaginal misoprostol for preabortion cervical priming: a randomized trial. Obstet Gynecol. 1999;94(3):431–4.

20. Meckstroth KR, Whitaker AK, Bertisch S, Goldberg AB, Darney PD. Misoprostol administered by epithelial routes: drug absorption and uterine response. Obstet Gynecol. 2006;108(3 Pt 1):582–90.

21. Borgatta L, Kapp N, Society of Family Planning. Clinical guidelines. Labor induction abortion in the second trimester. Contraception. 2011;84(1):4–18.

22. Goldberg A, Fortin JA, Drey EA, et al. Cervical preparation before dilation and evacuation using adjunctive misoprostol or mifepristone compared with overnight osmotic dilators alone: a randomized controlled trial. Obstet Gynecol. 2015;126:599–609.

23. Shaw KA, Shaw JG, Hugin M, Velasquez G, Hopkins FW, Blumenthal PD. Adjunct mifepristone for cervical preparation prior to dilation and evacuation: a randomized trial. Contraception. 2015;91(4):313–9.

24. Shaw KA, Lerma K, Shaw JG, et al. Preoperative effects of mifepristone for dilation and evacuation after 19 weeks of gestation: a randomised controlled trial. BJOG. 2017;124(13):1973–81.

25. American College of Obstetricians and Gynecologists, Society of Family Planning. Medical management of first-trimester abortion. Contraception. 2014;89(3):148–61.

26. Swahn ML, Bygdeman M. The effect of the antiprogestin RU 486 on uterine contractility and sensitivity to prostaglandin and oxytocin. Br J Obstet Gynaecol. 1988;95(2):126–34.

27. Creinin MD, Schreiber CA, Bednarek P, et al. Mifepristone and misoprostol administered simultaneously versus 24 hours apart for abortion: a randomized controlled trial. Obstet Gynecol. 2007;109(4):885–94.

28. Spitz IM, Bardin CW. Mifepristone (RU 486)—a modulator of progestin and glucocorticoid action. N Engl J Med. 1993;329(6):404–12.

29. Bygdeman M, Swahn ML, Gemzell-Danielsson K, Svalander P. Mode of action of RU 486. Ann Med. 1993;25(1):61–4.