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Mifepristone With Buccal Misoprostol for Medical Abortion

A Systematic Review

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OBJECTIVE: To summarize clinical outcomes and adverse effects of medical abortion regimens consisting of mifepristone followed by buccal misoprostol in pregnancies through 70 days of gestation.

DATA SOURCES: We used PubMed, ClinicalTrials.gov, and reference lists from published reports to identify relevant studies published between November 2005 and January 2015 using the search terms "mifepristone and medical abortion" and "buccal and misoprostol."

METHODS OF STUDY SELECTION: Studies were included if they presented clinical outcomes of medical abortion using mifepristone and buccal misoprostol through 70 days of gestation. Studies with duplicate data were excluded.

TABULATION, INTEGRATION, AND RESULTS: We included 20 studies with a total of 33,846 women through 70 days of gestation. We abstracted efficacy and ongoing pregnancy rates as an overall rate and by gestational age in days in reference to completed weeks (eg, 49 days or less, 50–56 days, 57–63 days, 64–70 days) and adverse effects when reported. The overall efficacy of mifepristone followed by buccal misoprostol is 96.7% (95% confidence interval [CI] 96.5–96.8%) and the continuing pregnancy rate is 0.8% (95% CI 0.7–0.9%) in approximately 33,000 pregnancies through 63 days of gestation. Only 332 women with pregnancies between 64 and 70 days of gestation are reported in the literature with an overall efficacy of 93.1% (95% CI 89.6–95.5%) and a continuing pregnancy rate of 2.9% (95% CI 1.4–5.7%). Currently available data suggest that regimens with a 24-hour time interval between mifepristone and buccal misoprostol administration are slightly less effective than those with a 24- to 48-hour interval. Rates of surgical evacuation for reasons other than ongoing pregnancy range from 1.8% to 4.2%. Severe adverse events like blood transfusion (0.03–0.6%) and hospitalization (0.04–0.9%) are uncommon.

CONCLUSION: Outpatient medical abortion regimens with mifepristone followed in 24–48 hours by buccal misoprostol are highly effective for pregnancy termination through 63 days of gestation. More data are needed to evaluate clinical outcomes with regimens containing mifepristone followed in 24 hours by buccal misoprostol and in pregnancies beyond 63 days of gestation.

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The use of medical abortion for pregnancy termination is increasing in the United States. In 2011, approximately 239,400 medical abortions were performed, which was a 20% increase from 2008.[1] The current U.S. Food and Drug Administration (FDA)–approved regimen for medical abortion consists of 600 mg mifepristone orally followed in 48 hours by 400 micrograms misoprostol orally in pregnancies up to 49 days based on initial clinical trials.[2] Studies since FDA approval in 2000 have accumulated evidence demonstrating increased efficacy in regimens with a lower dose of mifepristone and a higher dose of misoprostol, even in pregnancies past 49 days of gestation. The transition from oral to alternative routes of administration, including vaginal, buccal, and sublingual, is associated with increased efficacy and fewer side effects.[3,4] National evidence-based clinical guidelines in the United States, the United Kingdom, and other countries clearly identify that regimens other than the current FDA-approved regimen are superior based on higher efficacy and fewer adverse effects.[3,5]

See related editorial on page 3.

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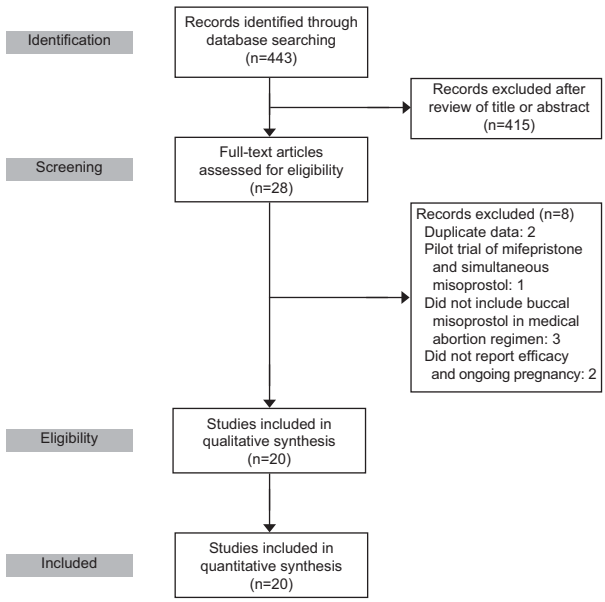

Fig. 1. Flow diagram of selected studies for systematic review.

Chen. Medical Abortion With Buccal Misoprostol. Obstet Gynecol 2015.

Vaginal misoprostol administration was routinely used in the United States until reports of severe infection with *Clostridium sordellii* after medical abortion surfaced,[6] prompting a reevaluation of vaginal misoprostol and a search for alternative routes of misoprostol administration. Although the use of vaginal misoprostol was ultimately not the cause of these infections, continued safety evaluations from Planned Parenthood Federation of America showed that severe infection, albeit a rare complication, decreased after changing to a buccal misoprostol regimen in addition to screening for sexually transmitted infections or providing routine preventive antibiotic coverage as part of the medical abortion.[7]

With buccal administration, misoprostol is held in the buccal pouch between the teeth and gums for 30 minutes before swallowing any remaining tablets. Buccal misoprostol is slowly absorbed, unlike oral misoprostol, which is rapidly absorbed and undergoes extensive first-pass metabolism. After a dose of oral misoprostol, plasma misoprostol acid levels peak quickly at 30 minutes and decrease rapidly by 120 minutes.[8] In contrast, after buccal administration, plasma misoprostol acid levels rise gradually to peak concentration after a median time of 75 minutes and fall slowly over several hours.[8–10]

Within the last 10 years, buccal misoprostol use with mifepristone for medical abortion has become commonplace. However, the published literature did not contain abundant information about medical abortion outcomes with buccal misoprostol until recently. In this systematic review, we summarize clinical outcomes and adverse effects of medical abortion regimens consisting of mifepristone followed by buccal misoprostol in pregnancies through 70 days of gestation.

SOURCES

We searched PubMed (http://www.ncbi.nlm.nih.gov/) for all relevant studies published from November 1, 2005, through January 31, 2015,

Table 1. Efficacy and Ongoing Pregnancy Rates With Mifepristone and Buccal Misoprostol for Medical Abortion Through 70 Days of Gestation

	Successful Abortion			Ongoing Pregnancy		
	No. in Analysis	No. Successful	% (95% CI)	No. in Analysis	No. of Ongoing Pregnancies	% (95% CI)
Overall						
Through 63 d of gestation	33,514	32,394	96.7 (96.5–96.8)	32,479	252	0.8 (0.7–0.9)
Through 70 d of gestation	33,846	32,703	96.6 (96.4–96.8)	32,785	261	0.8 (0.7–0.9)
By gestational age (d)*						
49 or less	12,555	12,318	98.1 (97.9–98.3)	10,781	40	0.4 (0.3–0.5)
50–56	4,161	4,024	96.7 (96.1–97.2)	4,008	34	0.8 (0.6–1.2)
57–63	2,202	2,096	95.2 (94.2–96.0)	2,119	39	1.8 (1.3–2.5)
64–70	332	309	93.1 (89.6–95.5)	306	9	2.9 (1.4–5.7)

CI, confidence interval.

All outcomes are based on patients for whom outcome was determined (patients without follow-up are not included).

* Not all studies reported outcome within each specific gestational age range; outcomes are calculated using only those studies with outcome data presented by gestational age.

Table 2. Efficacy and Ongoing Pregnancy Rates With Mifepristone Followed in 24 Hours by Buccal Misoprostol for Medical Abortion Through 63 Days of Gestation

Study, Location	Study Design	Gestational Age (d)	Oral Mifepristone Dose (mg)	Buccal Misoprostol Dose (micrograms)
Raghavan, 2010,[21] Maldova*	Prospective	63 or less	200	400
Giri, 2011,[17] Nepal	Prospective	63 or less	200	800
Ngoc, 2011,[18] Vietnam	Prospective	63 or less	200	800
Blum, 2012,[19] Tunisia, Vietnam	Prospective	63 or less	200	800
Dahiya, 2012,[20] India	Prospective	56 or less	200	800
Alam, 2013,[13] Bangladesh†	Prospective	63 or less	200	800
Total per category				

NR, not reported.
Data are n/N (%) unless otherwise specified.
All outcomes are based on patients for whom outcome was determined (patients without follow-up are not included).
* Five patients lost to follow-up in report without gestational age specified; all assumed to have gestational age 49 days or less for this review.
† Data were recalculated to present results only of those women who were pregnant at the time of receiving mifepristone and buccal misoprostol.

Table 3. Efficacy and Ongoing Pregnancy Rates With Mifepristone Followed in 24–48 Hours by Buccal Misoprostol for Medical Abortion Through 63 Days of Gestation

Study, Location	Study Design	Gestational Age (d)	Oral Mifepristone Dose (mg)	Buccal Misoprostol Dose (micrograms)	Time Interval Between Mifepristone and Misoprostol (h)
Middleton, 2005,[11] U.S.	Prospective	56 or less	200	800	24–48
Winikoff, 2008,[24] U.S.	Prospective	63 or less	200	800	24–36
Fjerstad, 2009,[22] U.S.*	Retrospective	59 or less	200	800	24–48
Boersma, 2011,[14] Curacao†	Prospective	63 or less	200	800	24–48
Grossman, 2011,[25] U.S.	Prospective	63 or less	200	800	24–48
Chong, 2012,[31] Georgia, Vietnam	Prospective	63 or less	200	400	36–48
				800	36–48
Goldstone, 2012,[26] Australia	Retrospective	63 or less	200	800	24–48
Ngo, 2012,[27] China	Retrospective	63 or less	200	800	36–48
Winikoff, 2012,[15] U.S.‡	Prospective	57–63	200	800	24–48
Chai, 2013,[23] Hong Kong§	Prospective	63 or less	200	800	48
Louie, 2014,[28] Azerbaijan	Prospective	63 or less	200	800	24–48
Ngoc, 2014,[29] Vietnam	Prospective	63 or less	200	800	24–48
Peña, 2014,[16] Mexico	Prospective	63 or less	200	800	24–48
Gatter, 2015,[30] U.S.	Retrospective	63 or less	200	800	24–48
Total per category					

NR, not reported.
Data are n/N (%) unless otherwise specified.
All outcomes are based on patients for whom outcome was determined (patients without follow-up are not included).
* Results in publication presented in categories of 28 or less, 28–34, 35–41, 42–48, 49–55, and 56–59 days of gestation. Results for women with pregnancies through 59 days included in overall clinical outcome analysis and only data from 48 days or less of gestation included into gestational age-specific results; outcomes for pregnancies 48 days or less were recalculated based on the manuscript text and table.
† Results in publication presented in categories of 49 or less, 50–63, and 64–70 days of gestation. Results for women with pregnancies through 63 days included in overall clinical outcome analysis and only data from 49 days or less of gestation included into gestational age-specific results.
‡ Study included women with pregnancies 57–70 days of gestation; only results for women with pregnancies 57–63 days of gestation included.
§ Results in publication presented in categories of 49 or less and 50–63 days of gestation; only data from 49 days or less of gestation included into gestational age-specific results.

Successful Abortion				Ongoing Pregnancy			
Overall	49 d or Less	50–56 d	57–63 d	Overall	49 d or Less	50–56 d	57–63 d
264/272 (97.1)	226/234 (96.6)	27/27 (100)	11/11 (100)	4/272 (1.5)	4/234 (1.7)	0/27 (0.0)	0/11 (0.0)
89/95 (93.6)	NR	NR	NR	1/95 (1.1)	NR	NR	NR
194/201 (96.5)	158/162 (97.5)	25/28 (89.3)	11/11 (100)	3/201 (1.5)	1/162 (0.6)	2/28 (7.1)	0/11 (0.0)
195/210 (92.9)	105/109 (96.3)	64/74 (86.5)	26/27 (96.3)	3/210 (1.4)	1/109 (0.9)	2/74 (2.7)	0/27 (0.0)
46/50 (92.0)	NR	NR	NR	0/50 (0.0)	NR	NR	NR
545/587 (92.8)	NR	NR	NR	NR	NR	NR	NR
1,333/1,415 (94.2)	489/505 (96.8)	116/129 (89.9)	48/49 (98.0)	11/828 (1.3)	6/505 (1.2)	4/129 (3.1)	0/49 (0.0)

examining the efficacy of mifepristone followed by buccal misoprostol for medical abortion through 70 days of gestation using the search terms "mifepristone and medical abortion" and "buccal and misoprostol." We used November 2005 as the earliest publication date limit because it is the known time of the first study reporting mifepristone followed by buccal misoprostol.[11] We also searched through

Successful Abortion, n/Total (%)				Ongoing Pregnancy, n/Total (%)			
Overall	49 d or Less	50–56 d	57–63 d	Overall	49 d or Less	50–56 d	57–63 d
205/216 (94.9)	NR	NR	NR	2/216 (0.9)	NR	NR	NR
405/421 (96.2)	207/213 (97.2)	89/93 (95.7)	109/115 (94.8)	4/421 (1.0)	2/213 (0.9)	0/93 (0.0)	2/115 (1.7)
1,326/1,349 (98.3)	946/961 (98.4)	NR	NR	6/1,349 (0.4)	NR	NR	NR
275/281 (97.9)	184/186 (98.9)	NR	NR	NR	NR	NR	NR
439/449 (97.8)	NR	NR	NR	4/449 (0.9)	NR	NR	NR
535/555 (96.4)	270/275 (98.2)	182/193 (94.3)	83/87 (95.4)	8/555 (1.4)	1/275 (0.4)	5/193 (2.6)	2/87 (2.3)
540/560 (96.4)	259/270 (95.9)	201/204 (98.5)	80/86 (93.0)	5/560 (0.9)	2/270 (0.7)	1/204 (0.5)	2/86 (2.3)
10,690/11,155 (96.5)	NR	NR	NR	83/11,155 (0.6)	NR	NR	NR
152/167 (91.0)	NR	NR	NR	NR	NR	NR	NR
304/325 (93.5)	NR	NR	304/325 (93.5)	10/325 (3.1)	NR	NR	10/325 (3.1)
43/45 (95.6)	22/22 (100)	NR	NR	0/45 (0.0)	0/22 (0.0)	NR	NR
840/863 (97.3)	608/627 (97.0)	152/153 (99.3)	80/83 (96.4)	7/863 (0.8)	NR	NR	NR
1,298/1,371 (94.7)	NR	NR	NR	36/1,371 (2.6)	NR	NR	NR
943/969 (97.3)	540/551 (98.0)	239/247 (96.8)	164/171 (95.9)	6/969 (0.6)	3/551 (0.6)	1/247 (0.4)	2/171 (1.2)
13,066/13,373 (97.7)	8,793/8,945 (98.3)	3,045/3,142 (96.9)	1,228/1,286 (95.5)	70/13,373 (0.5)	26/8,945 (0.3)	23/3,142 (0.7)	21/1,286 (1.6)
31,061/32,099 (96.8)	11,829/12,050 (98.2)	3,908/4,032 (96.9)	2,048/2,153 (95.1)	241/31,651 (0.8)	34/10,276 (0.3)	30/3,879 (0.8)	39/2,070 (1.9)

Table 4. Outcomes After a Repeat Dose of Misoprostol for Persistent Gestational Sac After Initial Treatment With Mifepristone and Buccal Misoprostol Through 63 Days of Gestation

Study, Country	Gestational Age (d)	Buccal Misoprostol Dose (micrograms)	Interval Between Mifepristone and Misoprostol (h)	Total No. of Patients	Eligible for 2nd Dose of Misoprostol	Chose to Have 2nd Dose of Misoprostol	Success After 2nd Dose of Misoprostol
Raghavan, 2010,[21] Maldova	63 or less	400	24	277	5 (1.8)	2 (40.0)	2 (100.0)
Winikoff, 2008,[24] U.S.	63 or less	800	24–36	421	NR	14*	13 (92.9)
Winikoff, 2012,[15] U.S.†	57–63	800	24–48	325	17 (5.2)	13 (76.5)	10 (91.0)‡
Louie, 2014,[28] Azerbaijan	63 or less	800	24–48	863	28 (3.2)	16 (57.1)	16 (100.0)

NR, not reported.
Data are n (%) unless otherwise specified.
All patients received regimens with 200 mg mifepristone orally.
* Unable to calculate percent success because the number of women eligible for a second dose of misoprostol was not reported.
† Study included women with pregnancies through 70 days of gestation; only results for women with pregnancies through 63 days of gestation included.
‡ Only 11 participants waited 1 week for evaluation and were used in the study to calculate success.

the reference sections of all identified manuscripts for other relevant studies. Lastly, we reviewed ClinicalTrials.gov (www.clinicaltrials.gov) for any completed randomized clinical trials that used mifepristone and buccal misoprostol in their protocol for medical abortion.

STUDY SELECTION

Only manuscripts discussing use of mifepristone and buccal misoprostol for medical abortion through 10 weeks of gestation were eligible for inclusion. Studies were excluded if clinical outcomes were not reported. If more than one study was published with duplicate data, only the study with the larger data set was included.

Both authors independently extracted study information, including the first author, year of publication, country in which the study was performed, study design, gestational age of the study population, number of patients enrolled and with follow-up,

Table 5. Complication Rates After Medical Abortion Through 63 Days of Gestation With Mifepristone and Buccal Misoprostol as Compared With Mifepristone and Oral Misoprostol

Study, Country	Gestational Age (d)	Mifepristone Dose (mg)	Misoprostol Dose (micrograms), Route	Interval Between Mifepristone and Misoprostol (h)
Middleton, 2005,[11] U.S.	56 or less	200	800, buccally	24–48
Winikoff, 2008,[24] U.S.	63 or less	200	800, buccally	24–36
Goldstone, 2012,[26] Australia	63 or less	200	800, buccally	24–48
Winikoff, 2012,[15] U.S.‡	63 or less	200	800, buccally	24–48
Gatter, 2015,[30] U.S.	63 or less	200	800, buccally	24–48
Spitz, 1998,[2] U.S.	63 or less	600	400, orally	48

ED, emergency department; NR, not reported.
Data are % unless otherwise specified.
All mifepristone administered orally.
* Reasons include medically necessary, incomplete abortion, persistent sac, and patient request.
† Four patients (1.9%) required intravenous fluids, but it was not specified if these patients were treated in the emergency department or required hospitalization.
‡ Study included women with pregnancies through 70 days of gestation; only results for women with pregnancies through 63 days of gestation are included.
§ Rate was 6.9% in a subset of 827 women through 49 days of gestation.

regimen used including repeat misoprostol dosing, and outcomes related to treatment efficacy, ongoing pregnancy rates, complications, and side effects.

Efficacy and ongoing pregnancy rates were abstracted as an overall rate and also categorized by gestational age in days in reference to completed weeks (eg, 49 days or less, 50–56 days, 57–63 days, 64–70 days). Efficacy is defined as complete expulsion of the pregnancy without need for surgical intervention. If study results were not presented in these categories, we recalculated, when possible, the gestational age-specific data based on tables and text within the manuscript. If we were unable to perform a reliable calculation, we excluded gestational age-specific data. Individual study outcomes were recalculated to exclude any patients who were not pregnant at the time of treatment. We then combined outcomes across studies to create summary statistics for efficacy and ongoing pregnancy as well as outcomes based on the interval between mifepristone and misoprostol administration.

Fisher's exact tests or χ^2 analyses were used to compare outcomes by gestational age, as appropriate. We considered a P value of .05 as statistically significant.

RESULTS

We identified 443 studies in the literature search and reviewed 28 full-text articles for eligibility. No additional studies were identified from searching the reference sections of the identified manuscripts or from clinicaltrials.gov. Eight records were excluded that had duplicate data (n=2), did not include buccal misoprostol in the medical abortion regimen (n=3), and did not report efficacy and ongoing pregnancy outcomes (n=2). We also excluded one additional study that was a pilot trial evaluating simultaneous dosing of mifepristone and buccal misoprostol and found clinically unacceptable success rates.[12] The 20 manuscripts in this review include a dosing interval of at least 24 hours between mifepristone and buccal misoprostol for medical abortions through 70 days of gestation. We followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for reporting of study selection (Fig. 1).

Primary outcome definitions were similar across the included studies. All of the studies defined successful abortion as one in which the pregnancy was expelled from the uterus without need for surgical evacuation during the follow-up period for any reason. Ongoing pregnancy was defined in all studies as a viable gestation at follow-up ultrasound evaluation performed per study protocol or when clinically indicated except one study that defined a viable gestation as an increase in uterine size on follow-up examination consistent with an ongoing pregnancy.[13]

The overall efficacy and continuing pregnancy rate after mifepristone followed by buccal misoprostol is 96.6% and 0.8%, respectively, through 70 days of gestation in the 33,846 women who were included in this systematic review (Table 1). However, only 332 women are reported in the literature between 64 and 70 days of gestation from three trials[14–16] with 304 of the patients from a single trial.[14] The overall efficacy at 64–70 days of gestation is 93.1%. Ongoing pregnancy rate at 64–70 days of gestation (n=306) is 2.9%

Total No. of Patients	Surgical Evacuation for Reasons Other Than Continuing Pregnancy*	Blood Transfusion	ED Visits	Hospitalization Related to Medical Abortion	Infection
216	4.2	0.5	NR†	NR†	0.5
421	2.9	NR	2.9	NR	NR
13,345	2.9	0.08	NR	NR	0.2
325	3.4	0.6	3.7	0.9	0.3
13,373	1.8	0.03	NR	0.04	0.01
2,015	8.9§	0.2	NR	1.3	0.9

Table 6. Reported Side-Effect Rates After Medical Abortion Through 63 Days of Gestation With Mifepristone and Buccal Misoprostol as Compared With Mifepristone and Oral Misoprostol

Study, Country	Gestational Age (d)	Mifepristone Dose (mg)	Misoprostol Dose (micrograms), Route	Interval Between Mifepristone and Misoprostol (h)
Middleton, 2005,[11] U.S.	56 or less	200	800, buccally	24–48
Winikoff, 2008,[24] U.S.	63 or less	200	800, buccally	24–36
Raghavan, 2010,[21] Maldova	63 or less	200	400, buccally	24
Ngoc, 2011,[18] Vietnam	63 or less	200	800, buccally	24
Chong, 2012,[31] Georgia, Vietnam	63 or less	200	400, buccally	36–48
			800, buccally	36–48
Winikoff, 2012,[15] U.S.*	63 or less	200	800, buccally	24–48
Blum, 2012,[19] Tunisia, Vietnam	63 or less	200	800 buccally	24
Dahiya, 2012,[20] India	56 or less	200	800, buccally	24
Chai, 2013,[23] Hong Kong	63 or less	200	800, buccally	48
Louie, 2014,[28] Azerbaijan	63 or less	200	800, buccally	24–48
Pena, 2014,[16] Mexico	More than 64†	200	800, buccally	24–48
Spitz, 1998,[2] U.S.	49 or less	600	400, orally	48
	63 or less			

NR, not reported.
Data are % unless otherwise specified.
All mifepristone administered orally.
* Study included women with pregnancies through 70 days of gestation; only results for women with pregnancies through 63 days of gestation included.
† Two patients were greater than 64 days of gestation; actual gestational age not reported.

as compared with 1.8% at 57–63 days of gestation (n=2,119) (P=.19).

Six studies (n=1,415) examined clinical outcomes when women were instructed to use buccal misoprostol 24 hours after mifepristone (Table 2). Gestational age-specific outcomes were reported in the literature for 505, 129, and 49 women with pregnancies 49 days or less, 50–56 days, and 57–63 days of gestation, respectively. All studies used a regimen with 200 mg mifepristone and 800 micrograms misoprostol buccally[13,17–20] except for one study that used 200 mg mifepristone and 400 micrograms misoprostol buccally.[21] Clinical outcomes for one study, which included women who were treated but were actually not pregnant, were recalculated to include only women who were pregnant.[13]

An additional 14 studies (n=32,099) examined clinical outcomes when women were instructed to use buccal misoprostol between 24 and 48 hours after mifepristone (Table 3). Gestational age-specific data were excluded from three studies that did not report their results in the prespecified gestational age ranges.[14,22,23] Outcomes by gestational age were reported for 12,050, 4,032, and 2,153 women with pregnancies 49 days or less, 50–56 days, and 57–63 days of gestation, respectively. All studies used 800 micrograms misoprostol buccally[11,14–16,22–30] except for one study that reported clinical outcomes with 400 micrograms misoprostol buccally.[31] One study described the actual time interval at which patients administered misoprostol after mifepristone, reporting a median interval of 48 hours (range 25–52 hours) for women who took mifepristone at home and a median interval of 47 hours (range 26–54 hours) for women that took mifepristone in the clinic.[28]

Success rates through 63 days of gestation from studies reporting a 24-hour interval between mifepristone and misoprostol differ significantly from the rates in studies with a 24- to 48-hour interval overall (94.2% compared with 96.8%, respectively, P<.001), among gestations 49 days or less (96.8% compared with 98.2%, respectively, P=.046) and gestations 50–63 days (92.1% compared with 96.3%, respectively, P=.009). Two studies included intervals of 36–48 hours[27,31] and one for 48 hours.[23] When these studies are excluded from the 24- to 48-hour group in the previous calculations, the results remain statistically significant for the overall (94.2% compared with 96.8%, respectively, P<.001), 49 days or less of gestation (96.8% compared with 98.2%, respectively, P=.04), and 50–63 days of gestation (92.1% compared with 96.3%, respectively, P=.008) calculations. The overall ongoing pregnancy rate through 63 days of gestation was not different among studies reporting a 24-hour or 24- to 48-hour interval between mifepristone and

Total No. of Patients	Nausea	Vomiting	Diarrhea	Weakness	Headache	Fever	Dizziness
216	69.4	37.0	36.1	54.6	43.5	42.1	40.7
414	75.1	47.6	43.0	58.0	41.1	47.6	39.4
266	54.1	22.2	NR	51.1	17.7	18.0	29.3
200	56.5	26.0	58.5	NR	NR	24.5	NR
555	44.0	16.0	NR	38.0	32.0	26.0	26.0
560	47.0	22.0	NR	42.0	33.0	33.0	24.0
318	50.0	35.8	17.9	NR	NR	11.9	NR
209	45.9	37.8	61.2	NR	NR	28.2	NR
50	64.0	16.0	8.0	NR	2.0	12.0	NR
45	46.7	20.0	31.1	NR	17.8	22.2	31.1
860	46.7	20.0	1.9	NR	NR	19.7	NR
969	34.0	26.0	60.0	21.0	14.0	45.0	13.0
859	61.5	25.8	20.3	NR	NR	NR	NR
1,851	67.3	33.9	22.9	NR	32.0	4.0	12.0

misoprostol (1.3% compared with 0.8%, respectively, P=.10).

Several studies using buccal misoprostol allowed the option of repeat misoprostol at follow-up 1 week after mifepristone for persistent gestational sac; however, few report specific outcomes. Table 4 highlights success rates after a repeat dose of misoprostol in reports that included these specific outcomes. In these study protocols, women with an ongoing pregnancy at follow-up were recommended to undergo uterine suction curettage, whereas women who had a nonviable pregnancy with a persistent gestational sac were given the options of expectant management, suction curettage, or a second dose of misoprostol. Overall, women who received a second dose of misoprostol experienced expulsion rates between 91.0% and 100.0%.

Adverse outcomes after medical abortion for selected studies are shown in Table 5. Rates of surgical evacuation for reasons other than ongoing pregnancy range from 1.8% to 4.2% in women who received mifepristone followed by buccal misoprostol, which is lower than the 6.9% surgical evacuation rate reported in women who received mifepristone followed by oral misoprostol through 49 days of gestation.[2] Blood transfusion and infection are uncommon, occurring in approximately 0.03–0.6% and 0.01–0.5% of patients, respectively. Adverse outcomes of emergency department visits (2.9–3.7%) and hospitalizations (0.04–0.9%) are inconsistently reported with variable rates across studies.

Reported treatment-associated side effects generally include nausea, vomiting, diarrhea, weakness, headache, dizziness, and thermoregulatory effects such as fevers and chills. Table 6 includes the rates of reported side effects after mifepristone and buccal misoprostol compared with mifepristone and oral misoprostol. Nausea rates after buccal misoprostol are generally slightly lower compared with oral misoprostol, whereas diarrhea, fever, and dizziness rates are higher among women who received buccal misoprostol.

DISCUSSION

Over 30,000 women have now been included in studies examining mifepristone with buccal misoprostol for medical abortion since the first report using this regimen 10 years ago. These studies demonstrate that outpatient medical abortion regimens with mifepristone followed in 24–48 hours by buccal misoprostol are highly effective for pregnancy termination through 63 days of gestation. The complete abortion rate with this protocol is higher than the 92% rate with the FDA-approved regimen.[2] Furthermore, surgical evacuation for reasons other than continuing pregnancy is also lower with buccal compared with oral misoprostol regimens. Side-effect rates vary across studies, which may be related to different ways of defining these events or different patient populations. Overall, the side-effect profile of both regimens is comparable, and regimens with buccal misoprostol have been shown to be well tolerated and acceptable to participants.[18,19,21,24]

Despite the presence of data supporting buccal misoprostol in medical abortion, there are still gaps in the literature, specifically with use 24 hours after mifepristone. Based on the available literature, the overall efficacy of regimens with a 24-hour interval

between mifepristone and buccal misoprostol is significantly lower than those with a 24- to 48-hour interval (94.2% compared with 98.1%). Our ability to fully understand if buccal misoprostol is more effective with a dosing interval closer to 48 hours is limited by the relatively small number of women in protocols with a 24-hour dosing as compared with a 24- to 48-hour dosing interval. Moreover, published trials only include outcomes by gestational age in 129 and 49 patients between 50–56 and 57–63 days of gestation, respectively. There is also a paucity of data on the actual time interval at which women actually administer misoprostol when instructed to use buccal misoprostol in a 24- to 48-hour window after mifepristone. Only one study reported the actual time elapsed between mifepristone and buccal misoprostol dosing; the median time interval was 47–48 hours.

Another obvious and important limitation of the available data is the relative lack of significant numbers of women who reported using mifepristone and buccal misoprostol beyond 63 days of gestation. Only 332 patients between 64 and 70 days of gestation are included in the literature, representing just 1.0% of the total number of women for which medical abortion outcomes with regimens containing buccal misoprostol are available. Based on current data, caution should be exercised when using buccal misoprostol in medical abortion regimens beyond 63 days in an outpatient setting until more evidence is available on efficacy rates and adverse effects.

Because regimens with mifepristone and buccal misoprostol are highly effective, large data sets are required to generate enough information to evaluate outcomes of a repeat misoprostol dose when abortion does not occur with initial treatment. These large data sets have been accumulated for regimens using vaginal misoprostol[32]; however, little information is available in the published literature about repeat dosing of buccal misoprostol (Table 4). These limited data do support the potential efficacy of a repeat dose of buccal misoprostol. Because most women who choose medical abortion have a strong desire to avoid surgery, further medical treatment instead of vacuum aspiration may be preferable as long as further medical management is beneficial. Although these studies did not report expulsion rates after expectant management, most women with a persistent gestational sac but absent gestational cardiac activity would eventually expel the pregnancy.[33] Even so, a repeat dose of misoprostol may facilitate quicker expulsion and is a reasonable option for women.

This study informs clinicians about the evidence supporting the use of mifepristone and buccal misoprostol for medical abortion. To our knowledge, this systematic review includes all studies that utilize mifepristone and buccal misoprostol for early medical abortion. Of note, the evidence for these regimens is mainly derived from two large retrospective studies that contribute 76% of the data on clinical outcomes.[26,30] To minimize heterogeneity of results, studies were grouped by the time interval between mifepristone and buccal misoprostol administration (ie, 24 hours and 24–48 hours) before analysis of overall efficacy and ongoing pregnancy rates. Further studies are needed to evaluate whether regimens with mifepristone followed in 24 hours by buccal misoprostol are effective, especially in pregnancies greater than 49 days of gestation. More evidence regarding clinical outcomes for pregnancies more than 63 days of gestation is needed before this practice becomes standard of care. With more high-quality data, women's health care providers can continue to provide the best evidence-based care to women.

REFERENCES

1. Jones RK, Jerman J. Abortion incidence and service availability in the United States, 2011. Perspect Sex Reprod Health 2014; 46:3–14.
2. Spitz IM, Bardin CW, Benton L, Robbins A. Early pregnancy termination with mifepristone and misoprostol in the United States. N Engl J Med 1998;338:1241–7.
3. Medical management of first-trimester abortion. Practice Bulletin No. 143. American College of Obstetricians and Gynecologists. Obstet Gynecol 2014;123:676–92.
4. Medical management of first-trimester abortion. Contraception 2014;89:148–61.
5. Royal College of Obstetricians and Gynaecologists. The care of women requesting induced abortion: evidence-based clinical guideline number 7. 3rd ed. London (UK): RCOG Press; 2011.
6. Fischer M, Bhatnagar J, Guarner J, Reagan S, Hacker JK, Van Meter SH, et al. Fatal toxic shock syndrome associated with Clostridium sordellii after medical abortion. N Engl J Med 2005;353:2352–60.
7. Trussell J, Nucatola D, Fjerstad M, Lichtenberg ES. Reduction in infection-related mortality since modifications in the regimen of medical abortion. Contraception 2014;89:193–6.
8. Tang OS, Schweer H, Seyberth HW, Lee SW, Ho PC. Pharmacokinetics of different routes of administration of misoprostol. Hum Reprod 2002;17:332–6.
9. Meckstroth KR, Whitaker AK, Bertisch S, Goldberg AB, Darney PD. Misoprostol administered by epithelial routes: drug absorption and uterine response. Obstet Gynecol 2006;108: 582–90.
10. Schaff EA, DiCenzo R, Fielding SL. Comparison of misoprostol plasma concentrations following buccal and sublingual administration. Contraception 2005;71:22–5.
11. Middleton T, Schaff E, Fielding SL, Scahill M, Shannon C, Westheimer T, et al. Randomized trial of mifepristone and

buccal or vaginal misoprostol for abortion through 56 days of last menstrual period. Contraception 2005;72:328–32.

12. Lohr PA, Reeves MF, Hayes JL, Harwood B, Creinin MD. Oral mifepristone and buccal misoprostol administered simultaneously for abortion: a pilot study. Contraception 2007;76: 215–20.
13. Alam A, Bracken H, Johnston HB, Raghavan S, Islam N, Winikoff B, et al. Acceptability and feasibility of mifepristone-misoprostol for menstrual regulation in Bangladesh. Int Perspect Sex Reprod Health 2013;39:79–87.
14. Boersma AA, Meyboom-de Jong B, Kleiverda G. Mifepristone followed by home administration of buccal misoprostol for medical abortion up to 70 days of amenorrhea in a general practice in Curacao. Eur J Contracept Reprod Health Care 2011;16:61–6.
15. Winikoff B, Dzuba IG, Chong E, Goldberg AB, Lichtenberg ES, Ball C, et al. Extending outpatient medical abortion services through 70 days of gestational age. Obstet Gynecol 2012;120:1070–6.
16. Peña M, Dzuba IG, Smith PS, Mendoza LJ, Bousiéguez M, Martinez ML, et al. Efficacy and acceptability of a mifepristone-misoprostol combined regimen for early induced abortion among women in Mexico City. Int J Gynaecol Obstet 2014;127:82–5.
17. Giri A, Tuladhar H, Tuladhar AS, Maharjan M, Dhakal N. Prospective study of medical abortion in Nepal Medical College Teaching Hospital (NMCTH). A one year experience. Nepal Med Coll J 2011;13:213–5.
18. Ngoc NT, Blum J, Raghavan S, Nga NT, Dabash R, Diop A, et al. Comparing two early medical abortion regimens: mifepristone+misoprostol vs. misoprostol alone. Contraception 2011;83:410–7.
19. Blum J, Raghavan S, Dabash R, Ngoc NT, Chelli H, Hajri S. Comparison of misoprostol-only and combined mifepristone-misoprostol regimens for home-based early medical abortion in Tunisia and Vietnam. Int J Gynaecol Obstet 2012;118:166–71.
20. Dahiya K, Ahuja K, Dhingra A, Duhan N, Nanda S. Efficacy and safety of mifepristone and buccal misoprostol versus buccal misoprostol alone for medical abortion. Arch Gynecol Obstet 2012;285:1055–8.
21. Raghavan S, Comendant R, Digol I, Ungureanu S, Dondiuc I, Turcanu S, et al. Comparison of 400 mcg buccal and 400 mcg sublingual misoprostol after mifepristone medical abortion through 63 days' LMP: a randomized controlled trial. Contraception 2010;82:513–9.
22. Fjerstad M, Sivin I, Lichtenberg ES, Trussell J, Cleland K, Cullins V. Effectiveness of medical abortion with mifepristone and buccal misoprostol through 59 gestational days. Contraception 2009;80:282–6.
23. Chai J, Wong CY, Ho PC. A randomized clinical trial comparing the short-term side effects of sublingual and buccal routes of misoprostol administration for medical abortions up to 63 days' gestation. Contraception 2013;87:480–5.
24. Winikoff B, Dzuba IG, Creinin MD, Crowden WA, Goldberg AB, Gonzales J, et al. Two distinct oral routes of misoprostol in mifepristone medical abortion: a randomized controlled trial. Obstet Gynecol 2008;112:1303–10.
25. Grossman D, Grindlay K, Buchacker T, Lane K, Blanchard K. Effectiveness and acceptability of medical abortion provided through telemedicine. Obstet Gynecol 2011; 118:296–303.
26. Goldstone P, Michelson J, Williamson E. Early medical abortion using low-dose mifepristone followed by buccal misoprostol: a large Australian observational study. Med J Aust 2012; 197:282–6.
27. Ngo TD, Park MH, Xiao Y. Comparing the World Health Organization-versus China-recommended protocol for first-trimester medical abortion: a retrospective analysis. Int J Womens Health 2012;4:123–7.
28. Louie KS, Tsereteli T, Chong E, Aliyeva F, Rzayeva G, Winikoff B. Acceptability and feasibility of mifepristone medical abortion in the early first trimester in Azerbaijan. Eur J Contracept Reprod Health Care 2014;19:457–64.
29. Ngoc NT, Bracken H, Blum J, Nga NT, Minh NH, van Nhang N, et al. Acceptability and feasibility of phone follow-up after early medical abortion in Vietnam: a randomized controlled trial. Obstet Gynecol 2014;123:88–95.
30. Gatter M, Cleland K, Nucatola DL. Efficacy and safety of medical abortion using mifepristone and buccal misoprostol through 63 days. Contraception 2015;91:269–73.
31. Chong E, Tsereteli T, Nguyen NN, Winikoff B. A randomized controlled trial of different buccal misoprostol doses in the mifepristone medical abortion. Contraception 2012;86:251–6.
32. Reeves MF, Kudva A, Creinin MD. Medical abortion outcomes after a second dose of misoprostol for persistent gestational sac. Contraception 2008;78:332–5.
33. Creinin MD, Danielsson KG. Medical abortion in early pregnancy. In: Paul M, Lichtenberg ES, Borgatta L, Grimes DA, Stubblefield PG, Creinin MD, editors. Management of unintended and abnormal pregnancy: comprehensive abortion care. 1st ed. Hoboken (NJ): Wiley-Blackwell; 2009. p. 111–34.