World Health Organization

Web annexes: Medical management of abortion: evidence summary*

3a. Medical management of induced abortion at < 12 weeks of gestation

* This publication forms part of the WHO guideline entitled *Medical management of abortion*. The full guideline and other web annexes are available at: https://www.who.int/reproductivehealth/publications/medical-management-abortion/en/

WHO/RHR/18.35

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Recommendation 3a: Medical management of induced abortion at < 12 weeks of gestation

I. Determine appropriate regimens for early medical abortion provision at ≤ 63 days

Comparison 1a: Mifepristone and misoprostol in combination compared with misoprostol alone

Summary of Findings table for Comparison 1a

Outcome	Anticipated absolute effect* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE) [1]	Comment
	Risk with misoprostol alone	Risk with combined mifepristone and misoprostol regimens				
Efficacy: ongoing pregnancy	139 per 1000	**22 per 1000** (11–43)	**RR 0.16** (0.08–0.31)	922 (3 RCTs) [1–3]	⊕⊕◯◯ LOW [a]	Our confidence in the direct estimate is limited; the true effect may be substantially different from the estimate of the effect
Efficacy: completed without surgical intervention	768 per 1000	**945 per 1000** (891–998)	**RR 1.23** (1.16–1.30)	922 (2 RCTs) [1,2]	⊕◯◯◯ VERY LOW [b,c]	We are uncertain about the effect on this outcome because the certainty of the evidence is very low
Efficacy: expulsion time	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies)	—	No direct evidence identified
Safety: serious adverse events and complications, such as hospitalization, blood transfusion, need for further surgery beyond interventions to complete the removal of products, or death	0 per 1000	**0 per 1000** (0–0)	Not estimable	(1 RCT) [1]	⊕◯◯◯ VERY LOW [a,b]	We are uncertain about the effect on this outcome because the certainty of the evidence is very low

[1] Grading of Recommendations Assessment, Development and Evaluation – more information: http://www.gradeworkinggroup.org

Outcome	Anticipated absolute effect * (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE) [1]	Comment
	Risk with misoprostol alone	Risk with combined mifepristone and misoprostol regimens				
Side-effects: bleeding	286 per 1000	**411 per 1000** (337–497)	**RR 1.44** (1.18–1.74)	805 (2 RCTs) [1,2]	⊕⊕◯◯ LOW [c]	Our confidence in the direct estimate is limited; the true effect may be substantially different from the estimate of the effect
Side-effects: pain	322 per 1000	**312 per 1000** (254–383)	**RR 0.97** (0.79–1.19)	805 (2 RCTs) [1,2]	⊕⊕◯◯ LOW [c,d]	Our confidence in the direct estimate is limited; the true effect may be substantially different from the estimate of the effect
Side-effects: vomiting	229 per 1000	**220 per 1000** (174–277)	**RR 0.96** (0.76–1.21)	820 (2 RCTs) [1,2]	⊕⊕⊕◯ MODERATE [d]	Use of combined mifepristone and misoprostol compared with misoprostol alone probably slightly reduces emesis
Satisfaction	747 per 1000	**844 per 1000** (747–941)	**RR 1.13** (1.00–1.26)	820 (2 RCTs) [1,2]	⊕⊕◯◯ LOW [d]	Our confidence in the direct estimate is limited; the true effect may be substantially different from the estimate of the effect

CI: confidence interval; RCT: randomized controlled trial; RR: risk ratio

* The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group grades of evidence

High certainty: We are very confident that the true effect is close to the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Downgraded two levels for imprecision: few events and broad 95% CI.
b. Unclear randomization and allocation strategy in the study by Dahiya et al. *(3)*.
c. Downgraded one level: outcome assessed differently across studies, both in terms of how and when it was measured.
d. Downgraded one level: data self-reported and subject to recall bias.

References

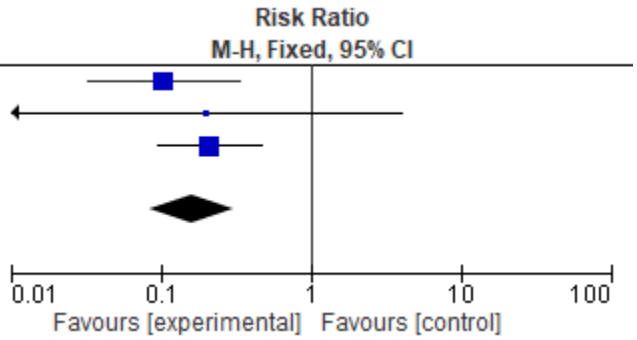
1. Blum J, Raghavan S, Dabash R, Ngoc Nguyen TN, Chelli H, Hajri S, et al. Comparison of misoprostol-only and combined mifepristone-misoprostol regimens for home-based early medical abortion in Tunisia and Vietnam. Int J Gynaecol Obstet. 2012;118(2):166-71.
2. Ngoc Nguyen TN, Blum J, Raghavan S, Nga Nguyen TB, Dabash R, Diop A, et al. Comparing two early medical abortion regimens: mifepristone + misoprostol vs. misoprostol alone. Contraception. 2011;83(5):410-7.
3. 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(4):1055-8.

Forest plots for Comparison 1a

Analysis 1. Efficacy: ongoing pregnancy

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Blum 2012	3	210	30	218	45.6%	0.10 [0.03, 0.34]
Dahiya 2012	0	50	2	50	3.9%	0.20 [0.01, 4.06]
Ngoc 2011	7	201	32	193	50.6%	0.21 [0.09, 0.46]
Total (95% CI)		**461**		**461**	**100.0%**	**0.16 [0.08, 0.31]**
Total events	10		64			

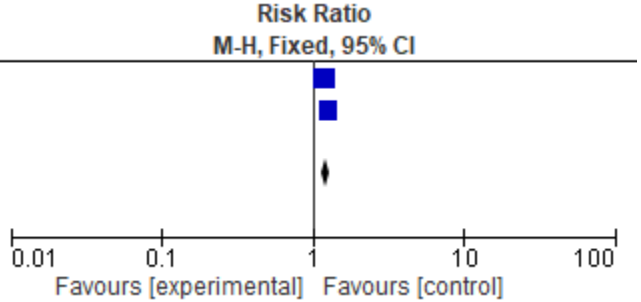
Heterogeneity: Chi² = 0.99, df = 2 (P = 0.61); I² = 0%
Test for overall effect: Z = 5.59 (P < 0.00001)



Analysis 2. Efficacy: completed without surgical intervention

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Blum 2012	195	210	170	218	52.7%	1.19 [1.10, 1.29]
Ngoc 2011	194	201	147	193	47.3%	1.27 [1.17, 1.38]
Total (95% CI)		**411**		**411**	**100.0%**	**1.23 [1.16, 1.30]**
Total events	389		317			

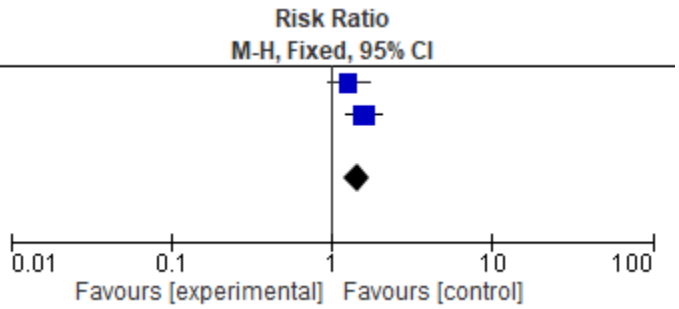
Heterogeneity: Chi² = 1.12, df = 1 (P = 0.29); I² = 11%
Test for overall effect: Z = 6.96 (P < 0.00001)



Analysis 3. Side-effects: bleeding

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Blum 2012	70	206	55	206	47.8%	1.27 [0.95, 1.71]
Ngoc 2011	97	200	59	193	52.2%	1.59 [1.23, 2.05]
Total (95% CI)		**406**		**399**	**100.0%**	**1.44 [1.18, 1.74]**
Total events	167		114			

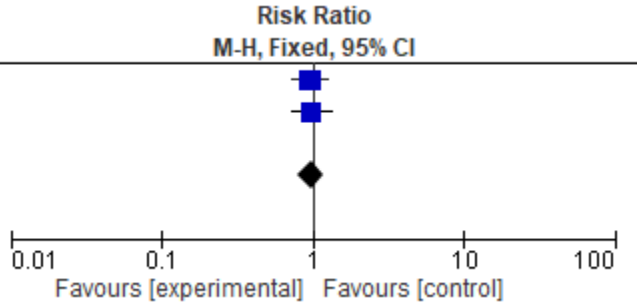
Heterogeneity: Chi² = 1.22, df = 1 (P = 0.27); I² = 18%
Test for overall effect: Z = 3.67 (P = 0.0002)



Analysis 4. Side-effects: pain

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Blum 2012	65	204	69	208	52.8%	0.96 [0.73, 1.27]
Ngoc 2011	61	200	60	193	47.2%	0.98 [0.73, 1.32]
Total (95% CI)		**404**		**401**	**100.0%**	**0.97 [0.79, 1.19]**
Total events	126		129			

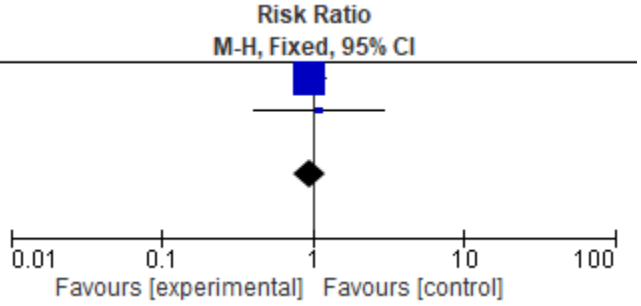
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.92); I² = 0%
Test for overall effect: Z = 0.29 (P = 0.77)



Analysis 5. Side-effects: vomiting

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Blum 2012	79	209	87	218	92.3%	0.95 [0.75, 1.20]
Ngoc 2011	8	200	7	193	7.7%	1.10 [0.41, 2.98]
Total (95% CI)		**409**		**411**	**100.0%**	**0.96 [0.76, 1.21]**
Total events	87		94			

Heterogeneity: Chi² = 0.09, df = 1 (P = 0.77); I² = 0%
Test for overall effect: Z = 0.35 (P = 0.73)

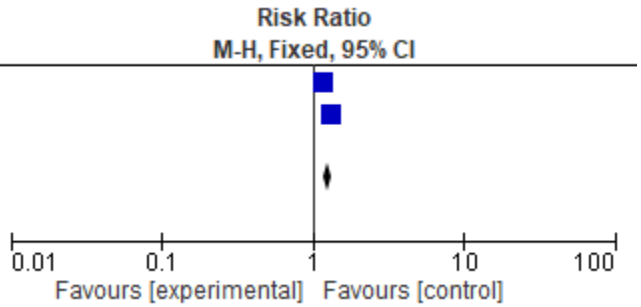


Analysis 6. Satisfaction

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Blum 2012	188	209	166	218	53.1%	1.18 [1.08, 1.29]
Ngoc 2011	193	200	141	193	46.9%	1.32 [1.21, 1.44]
Total (95% CI)		**409**		**411**	**100.0%**	**1.25 [1.17, 1.33]**
Total events	381		307			

Heterogeneity: $Chi^2 = 3.07$, df = 1 (P = 0.08); $I^2 = 67\%$

Test for overall effect: Z = 6.93 (P < 0.00001)



Comparison 1b: Mifepristone and vaginal misoprostol in combination compared with 800 µg vaginal misoprostol alone

Summary of Findings table for Comparison 1b

Outcome	Anticipated absolute effect* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comment
	Risk with 800 µg vaginal misoprostol	Risk with combined mifepristone and vaginal misoprostol				
Efficacy: ongoing pregnancy	51 per 1000	**5 per 1000** (1–41)	**RR 0.10** (0.01–0.80)	344 (2 RCTs) [1,2]	⊕◯◯◯ VERY LOW [a,b]	We are uncertain about the effect on this outcome because the certainty of the evidence is very low
Efficacy: completed without surgical intervention	860 per 1000	**903 per 1000** (671–1000)	**RR 1.05** (0.78–1.41)	100 (1 RCT) [1]	⊕◯◯◯ VERY LOW [a,c,d]	We are uncertain about the effect on this outcome because the certainty of the evidence is very low
Efficacy: expulsion time	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies)	—	No direct evidence identified
Safety: serious adverse events and complications, such as hospitalization, blood transfusion, need for further surgery beyond interventions to complete the removal of products, or death	0 per 1000	**0 per 1000** (0–0)	**RR 1.05** (0.02–52.49)	244 (1 RCT) [2]	⊕◯◯◯ VERY LOW [a,b,c]	We are uncertain about the effect on this outcome because the certainty of the evidence is very low
Side-effects: bleeding	220 per 1000	**24 per 1000** (2–178)	**RR 0.11** (0.01–0.81)	100 (1 RCT) [1]	⊕◯◯◯ VERY LOW [a,d,e]	We are uncertain about the effect on this outcome because the certainty of the evidence is very low
Side-effects: pain	171 per 1000	**171 per 1000** (106–274)	**RR 1.00** (0.62–1.60)	344 (2 RCTs) [1,2]	⊕◯◯◯ VERY LOW [a,d,e]	We are uncertain about the effect on this outcome because the certainty of the evidence is very low
Side-effects: vomiting	211 per 1000	**326 per 1000** (226–465)	**RR 1.54** (1.07–2.20)	344 (2 RCTs) [1,2]	⊕◯◯◯ VERY LOW [a,d,e]	We are uncertain about the effect on this outcome because the certainty of the evidence is very low

Outcome	Anticipated absolute effect* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comment
	Risk with 800 µg vaginal misoprostol	Risk with combined mifepristone and vaginal misoprostol				
Satisfaction	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies)	—	No direct evidence identified

CI: confidence interval; RCT: randomized controlled trial; RR: risk ratio
* The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect is close to the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Explanations

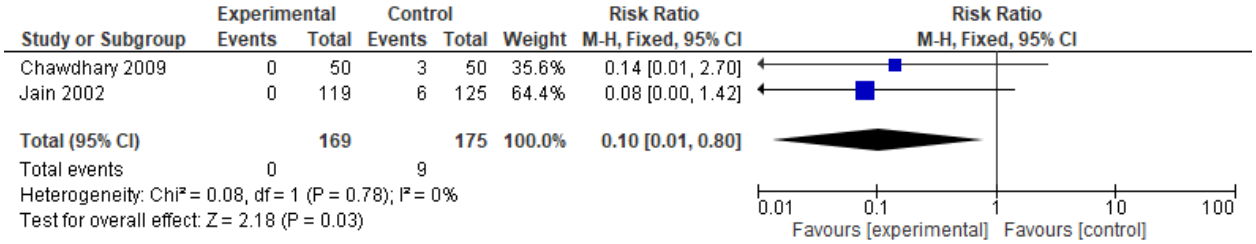
a. Quasi-randomized trial with inadequate description of randomization scheme and high risk for selection bias.
b. Downgraded one level for imprecision: few events and broad 95% CI.
c. Downgraded one level for inconsistency: only one trial included.
d. Downgraded two levels for imprecision: few events and broad 95% CI.
e. Outcomes measured differently and at different time points across studies.

References

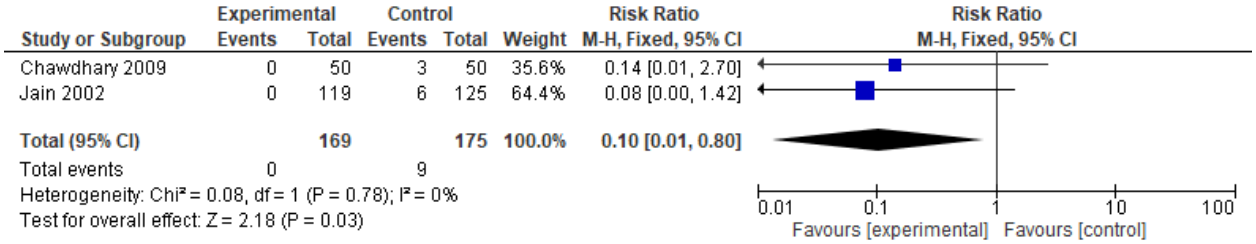
1. Chawdhary R, Rana A, Pradhan N. Mifepristone plus vaginal misoprostol vs vaginal misoprostol alone for medical abortion in gestation 63 days or less in Nepalese women: a quasi-randomized controlled trial. J Obstet Gynaecol Res. 2009;35(1):78-85.
2. Jain JK, Dutton C, Harwood B, Meckstroth KR, Mishell DR, Jr. A prospective randomized, double-blinded, placebo-controlled trial comparing mifepristone and vaginal misoprostol to vaginal misoprostol alone for elective termination of early pregnancy. Hum Reprod. 2002;17(6):1477-82.

Forest plots for Comparison 1b

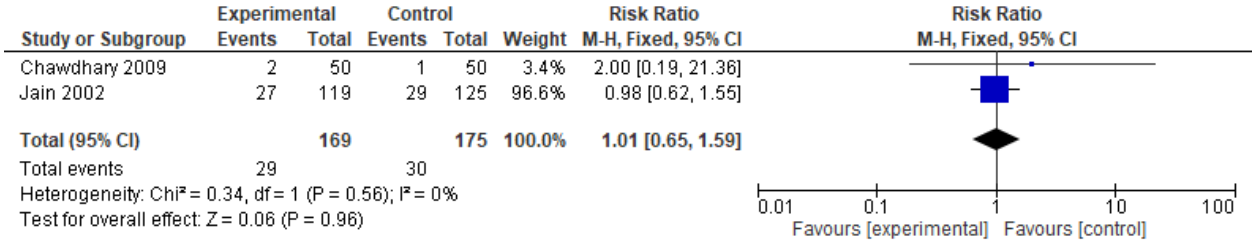
Analysis 1. Efficacy: ongoing pregnancy



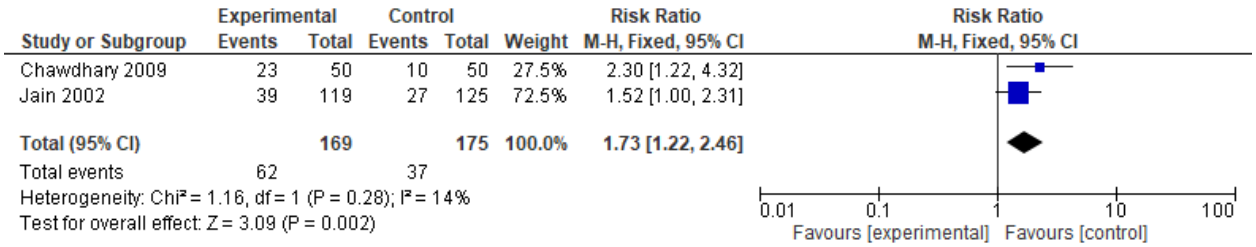
Analysis 2. Efficacy: completed without surgical intervention



Analysis 3. Side-effects: pain



Analysis 4. Side-effects: vomiting



Comparison 1c: Mifepristone (200 mg oral) and misoprostol (400 µg oral) in combination compared with 800 µg sublingual misoprostol alone every 4 hours

Summary of Findings table for Comparison 1c

Outcome	Anticipated absolute effect* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comment
	Risk with 800 µg sublingual misoprostol every 4 h	Risk with 200 mg oral mifepristone and 400 µg oral misoprostol				
Efficacy: ongoing pregnancy	8 per 1000	**8 per 1000** (0–125)	**RR 1.00** (0.06–15.81)	252 (1 RCT) [1]	⊕◯◯◯ VERY LOW [a–c]	We are uncertain about the effect on this outcome because the certainty of the evidence is very low
Efficacy: completed without surgical intervention	921 per 1000	**930 per 1000** (773–1000)	**RR 1.01** (0.84–1.21)	252 (1 RCT) [1]	⊕◯◯◯ VERY LOW [a,b,d]	We are uncertain about the effect on this outcome because the certainty of the evidence is very low
Efficacy: expulsion time	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies)	—	No direct evidence identified
Safety: serious adverse events and complications, such as hospitalization, blood transfusion, need for further surgery beyond interventions to complete the removal of products, or death	0 per 1000	**0 per 1000** (0–0)	**RR 1.00** (0.02–50.01)	252 (1 RCT) [1]	⊕◯◯◯ VERY LOW [a,b,d]	We are uncertain about the effect on this outcome because the certainty of the evidence is very low
Side-effects: bleeding	63 per 1000	**99 per 1000** (43–232)	**RR 1.56** (0.67–3.65)	252 (1 RCT) [1]	⊕◯◯◯ VERY LOW [a,b,d]	We are uncertain about the effect on this outcome because the certainty of the evidence is very low
Side-effects: pain	373 per 1000	**269 per 1000** (179–403)	**RR 0.72** (0.48–1.08)	252 (1 RCT) [1]	⊕⊕◯◯ LOW [a,b,d]	Our confidence in the direct estimate is limited; the true effect may be substantially different from the estimate of the effect

Outcome	Anticipated absolute effect * (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comment
	Risk with 800 µg sublingual misoprostol every 4 h	Risk with 200 mg oral mifepristone and 400 µg oral misoprostol				
Side-effects: vomiting	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies)	—	No direct evidence identified
Satisfaction	921 per 1000	**939 per 1000** (783–1000)	**RR 1.02** (0.85–1.22)	252 (1 RCT) [1]	⨁◯◯◯ VERY LOW [a,b,d]	We are uncertain about the effect on this outcome because the certainty of the evidence is very low

CI: confidence interval; RCT: randomized controlled trial; RR: risk ratio

* The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect is close to the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Downgraded for high risk of reporting and detection biases.
b. Results not separated by number of doses of misoprostol received by women in the comparison arm.
c. Downgraded two levels in imprecision: small numbers and broad 95% CI.
d. Downgraded one level in imprecision: small numbers and broad 95% CI.

Reference

1. Fekih M, Fathallah K, Ben Regaya L, Bouguizane S, Chaieb A, Bibi M, et al. Sublingual misoprostol for first trimester termination of pregnancy. Int J Gynaecol Obstet. 2010;109(1):67-70.

Comparison 2a: Doses of misoprostol in combination regimens (mifepristone plus misoprostol): 400 µg compared with 800 µg buccal misoprostol

Summary of Findings table for Comparison 2a

Outcome	Anticipated absolute effect* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comment
	Risk with 200 mg mifepristone with 800 µg buccal misoprostol	Risk with 200 mg mifepristone with 400 µg buccal misoprostol				
Efficacy: ongoing pregnancy	9 per 1000	**1 per 1000** (1–3)	**RR 0.16** (0.08–0.31)	1115 (1 RCT) [1]	⊕⊕⊕◯ MODERATE [a]	Use of 400 µg compared with 800 µg misoprostol buccally probably slightly reduces the risk of ongoing pregnancy
Efficacy: completed without surgical intervention	964 per 1000	**1000 per 1000** (1000–1000)	**RR 1.23** (1.16–1.30)	1115 (1 RCT) [1]	⊕⊕⊕◯ MODERATE [a]	Use of 400 µg compared with 800 µg misoprostol buccally probably slightly reduces the risk of being completed without surgical intervention
Efficacy: expulsion time	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies)	—	
Safety: serious adverse events and complications, such as hospitalization, blood transfusion, need for further surgery beyond interventions to complete the removal of products, or death	0 per 1000	**0 per 1000** (0–0)	**RR 1.00** (0.02–50.76)	1115 (1 RCT) [1]	⊕⊕⊕◯ MODERATE [a]	Use of 800 µg compared with 400 µg misoprostol buccally probably does not alter the risk of serious adverse events
Side-effects: bleeding	11 per 1000	**15 per 1000** (13–19)	**RR 1.44** (1.18–1.74)	1115 (1 RCT) [1]	⊕⊕◯◯ LOW [a,b]	Our confidence in the direct estimate is limited; the true effect may be substantially different from the estimate of the effect
Side-effects: pain	809 per 1000	**777 per 1000** (728–825)	**RR 0.96** (0.90–1.02)	1115 (1 RCT) [1]	⊕⊕◯◯ LOW [a,b]	Our confidence in the direct estimate is limited; the true effect may be substantially different from the estimate of the effect

Outcome	Anticipated absolute effect * (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comment
	Risk with 200 mg mifepristone with 800 µg buccal misoprostol	Risk with 200 mg mifepristone with 400 µg buccal misoprostol				
Side-effects: vomiting	220 per 1000	**158 per 1000** (123–202)	**RR 0.72** (0.56–0.92)	1115 (2 RCTs) [2,3]	⊕⊕◯◯ LOW [a,b]	Our confidence in the direct estimate is limited; the true effect may be substantially different from the estimate of the effect
Satisfaction	962 per 1000	**953 per 1000** (933–981)	**RR 0.99** (0.97–1.02)	1106 (2 RCTs) [2,3]	⊕◯◯◯ VERY LOW [a,b]	We are uncertain about the effect on this outcome because the certainty of the evidence is very low

CI: confidence interval; RCT: randomized controlled trial; RR: risk ratio
* The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect is close to the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Explanations
a. Gestational ages enrolled varied by country.
b. Downgraded one level: data self-reported and subject to recall bias.

References

1. Chong E, Tsereteli T, Nguyen NN, Winikoff B. A randomized controlled trial of different buccal misoprostol doses in mifepristone medical abortion. Contraception . 2012;86(3):251-6.
2. Blum J, Raghavan S, Dabash R, Ngoc Nguyen TN, Chelli H, Hajri S, et al. 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(2):166-71.
3. Ngoc Nguyen TN, Blum J, Raghavan S, Nga Nguyen TB, Dabash R, Diop A, et al. Comparing two early medical abortion regimens: mifepristone + misoprostol vs. misoprostol alone. Contraception. 2011;83(5):410-7.

Comparison 2b: Doses of misoprostol in combination regimens (mifepristone plus misoprostol): 400 µg oral misoprostol twice compared with once

Summary of Findings table for Comparison 2b

Outcome	Anticipated absolute effect* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comment
	Risk with 200 mg mifepristone and 400 µg oral misoprostol once	Risk with 200 mg mifepristone and 400 µg oral misoprostol twice				
Efficacy: ongoing pregnancy	68 per 1000	**7 per 1000** (1–54)	**RR 0.10** (0.01–0.80)	297 (1 RCT) [1]	⊕⊕◯◯ LOW [a,b]	Our confidence in the direct estimate is limited; the true effect may be substantially different from the estimate of the effect
Efficacy: completed without surgical intervention	864 per 1000	**890 per 1000** (743–1000)	**RR 1.03** (0.86–1.23)	297 (1 RCT) [1]	⊕⊕◯◯ LOW [a,b]	Our confidence in the direct estimate is limited; the true effect may be substantially different from the estimate of the effect
Efficacy: expulsion time	0 per 1000	**0 per 1000** (0–0)	Not estimable	(1 RCT) [1]	—	Expulsion time for the intervention group was 179.21 min, compared with 193.91 min for the single-dose group
Safety: serious adverse events and complications, such as hospitalization, blood transfusion, need for further surgery beyond interventions to complete the removal of products, or death	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies)	—	No direct evidence identified
Side-effects: bleeding	553 per 1000	**548 per 1000** (426–703)	**RR 0.99** (0.77–1.27)	300 (1 RCT) [1]	⊕⊕◯◯ LOW [a,b]	Our confidence in the direct estimate is limited; the true effect may be substantially different from the estimate of the effect
Side-effects: pain	873 per 1000	**882 per 1000** (734–1000)	**RR 1.01** (0.84–1.20)	300 (1 RCT) [1]	⊕⊕◯◯ LOW [a,b]	Our confidence in the direct estimate is limited; the true effect may be substantially different from the estimate of the effect

Outcome	Anticipated absolute effect * (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comment
	Risk with 200 mg mifepristone and 400 µg oral misoprostol once	Risk with 200 mg mifepristone and 400 µg oral misoprostol twice				
Side-effects: vomiting	0 per 1000	**0 per 1000** (0–0)	**RR 1.00** (0.02–50.00)	300 (1 RCT) [1]	⊕⊕◯◯ LOW [a,b]	Our confidence in the direct estimate is limited; the true effect may be substantially different from the estimate of the effect
Satisfaction	882 per 1000	**908 per 1000** (767–1000)	**RR 1.03** (0.87–1.23)	293 (1 RCT) [1]	⊕⊕◯◯ LOW [a,b]	Our confidence in the direct estimate is limited; the true effect may be substantially different from the estimate of the effect

CI: confidence interval; RCT: randomized controlled trial; RR: risk ratio
* The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect is close to the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Explanations
a. Downgraded one level for inconsistency: only one trial included.
b. Downgraded one level for imprecision: few events and broad 95% CI.

References
1. Coyaji K, Krishna U, Ambardekar S, Bracken H, Raote V, Mandlekar A, et al. Are two doses of misoprostol after mifepristone for early abortion better than one? BJOG. 2007;114(3):271-8.

Comparison 2c: Doses of misoprostol in combination regimens (mifepristone plus misoprostol): 800 µg oral misoprostol once compared with 400 µg oral misoprostol twice

Summary of Findings table for Comparison 2c

Outcome	Anticipated absolute effect* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comment
	Risk with mifepristone and 400 µg oral misoprostol twice	Risk with mifepristone and 800 µg oral misoprostol once				
Efficacy: ongoing pregnancy	15 per 1000	**13 per 1000** (3–47)	**RR 0.88** (0.24–3.19)	637 (2 RCTs) [1,2]	⊕⊕⊕◯ MODERATE [a]	There is probably no difference in this outcome when 400 µg oral misoprostol is used twice compared with 800 µg once
Efficacy: completed without surgical intervention	918 per 1000	**863 per 1000** (817–909)	**RR 0.94** (0.89–0.99)	637 (2 RCTs) [1,2]	⊕⊕⊕◯ MODERATE [a]	There is probably a slightly reduced risk of the procedure being completed without surgical intervention when 400 µg oral misoprostol is used twice compared with 800 µg once
Efficacy: expulsion time	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies)	—	No direct evidence identified
Safety: serious adverse events and complications, such as hospitalization, blood transfusion, need for further surgery beyond interventions to complete the removal of products, or death	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies)	—	No direct evidence identified
Side-effects: bleeding	40 per 1000	**27 per 1000** (4–157)	**RR 0.67** (0.11–3.93)	150 (1 RCT) [1]	⊕◯◯◯ VERY LOW [b,c]	We are uncertain about the effect on this outcome because the certainty of the evidence is very low
Side-effects: pain	387 per 1000	**363 per 1000** (232–572)	**RR 0.94** (0.60–1.48)	150 (1 RCT) [1]	⊕◯◯◯ VERY LOW [b,c]	We are uncertain about the effect on this outcome because the certainty of the evidence is very low

Outcome	Anticipated absolute effect * (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comment
	Risk with mifepristone and 400 µg oral misoprostol twice	Risk with mifepristone and 800 µg oral misoprostol once				
Side-effects: vomiting	307 per 1000	**371 per 1000** (233–595)	**RR 1.21** (0.76–1.94)	150 (1 RCT) [1]	⨁◯◯◯ VERY LOW [b,c]	We are uncertain about the effect on this outcome because the certainty of the evidence is very low
Satisfaction	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies)	—	No direct evidence identified

CI: confidence interval; RCT: randomized controlled trial; RR: risk ratio

* The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect is close to the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Non-blinding of participants, providers and outcome assessors.
b. Downgraded one level for inconsistency: only one trial included.
c. Downgraded two levels in imprecision: small numbers and broad 95% CI.

References

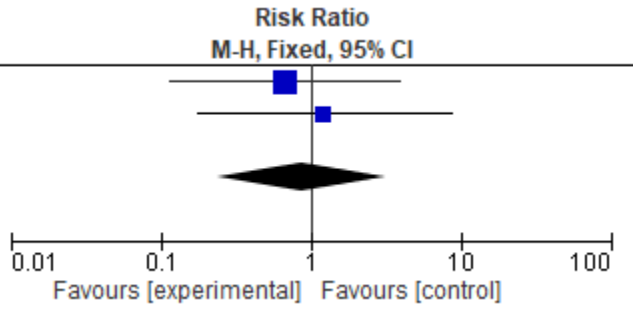
1. el-Refaey H, Templeton A. Early abortion induction by a combination of mifepristone and oral misoprostol: a comparison between two dose regimens of misoprostol and their effect on blood pressure. Br J Obstet Gynaecol. 1994;101(9):792-6.
2. Schaff EA, Fielding SL, Westhoff C. Randomized trial of oral versus vaginal misoprostol 2 days after mifepristone 200 mg for abortion up to 63 days of pregnancy. Contraception. 2002;66(4):247-50.

Forest plots for Comparison 2c

Analysis 1. Efficacy: ongoing pregnancy

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
El-Regaey 1994	2	75	3	75	62.5%	0.67 [0.11, 3.88]
Schaff 2002	2	219	2	268	37.5%	1.22 [0.17, 8.62]
Total (95% CI)		**294**		**343**	**100.0%**	**0.88 [0.24, 3.19]**
Total events	4		5			

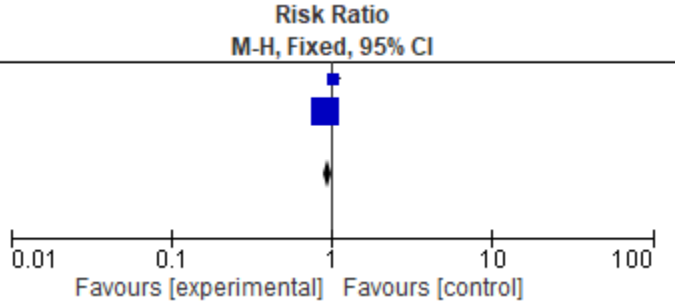
Heterogeneity: Chi² = 0.21, df = 1 (P = 0.65); I² = 0%
Test for overall effect: Z = 0.20 (P = 0.84)



Analysis 2. Efficacy: completed without surgical intervention

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
El-Regaey 1994	71	75	69	75	23.8%	1.03 [0.94, 1.12]
Schaff 2002	183	219	246	268	76.2%	0.91 [0.85, 0.98]
Total (95% CI)		**294**		**343**	**100.0%**	**0.94 [0.89, 0.99]**
Total events	254		315			

Heterogeneity: Chi² = 5.18, df = 1 (P = 0.02); I² = 81%
Test for overall effect: Z = 2.22 (P = 0.03)



Comparison 2d: Doses of misoprostol in combination regimens (mifepristone plus misoprostol): 400 µg compared with 800 µg sublingual misoprostol

Summary of Findings table for Comparison 2d

Outcome	Anticipated absolute effect * (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comment
	Risk with 800 µg sublingual misoprostol	Risk with 400 µg sublingual misoprostol				
Efficacy: ongoing pregnancy	5 per 1000	**19 per 1000** (6–56)	**RR 3.44** (1.14–10.40)	1480 (1 RCT) [1]	⊕⊕⊕◯ MODERATE [a]	There is probably a slightly increased risk of ongoing pregnancy when 400 µg versus 800 µg misoprostol is used sublingually
Efficacy: completed without surgical intervention	939 per 1000	**930 per 1000** (864–1000)	**RR 0.99** (0.92–1.07)	1480 (1 RCT) [1]	⊕⊕⊕◯ MODERATE [a]	There is probably no difference in this outcome when a dose of 400 µg versus 800 µg of misoprostol is used sublingually
Efficacy: expulsion time	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies)	—	No direct evidence identified
Safety: serious adverse events and complications, such as hospitalization, blood transfusion, need for further surgery beyond interventions to complete the removal of products, or death	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies) [b]	—	No direct evidence identified
Side-effects: bleeding	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies) [b]	—	No direct evidence identified
Side-effects: pain	987 per 1000	**987 per 1000** (918–1000)	**RR 1.00** (0.93–1.07)	1501 (1 RCT) [1]	⊕⊕◯◯ LOW [a,c]	Our confidence in the direct estimate is limited; the true effect may be substantially different from the estimate of the effect
Side-effects: vomiting	256 per 1000	**358 per 1000** (291–440)	**RR 1.40** (1.14–1.72)	1501 (1 RCT) [1]	⊕⊕◯◯ LOW [a,c]	Our confidence in the direct estimate is limited; the true effect may be substantially different from the estimate of the effect

Outcome	Anticipated absolute effect * (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comment
	Risk with 800 µg sublingual misoprostol	Risk with 400 µg sublingual misoprostol				
Satisfaction	936 per 1000	**927 per 1000** (861–1000)	**RR 0.99** (0.92–1.07)	1475 (1 RCT) [1,d]	⊕⊕◯◯ LOW [a,c]	Our confidence in the direct estimate is limited; the true effect may be substantially different from the estimate of the effect

CI: confidence interval; RCT: randomized controlled trial; RR: risk ratio
* The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect is close to the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Downgraded one level: results from only one trial.
b. Data not disaggregated by this comparison.
c. Subject to recall and/or courtesy bias.
d. Answered "highly satisfied".

References

1. von Hertzen H, Huong NT, Piaggio G, Bayalag M, Cabezas E, Fang AH, et al. Misoprostol dose and route after mifepristone for early medical abortion: a randomised controlled noninferiority trial. BJOG. 2010;117(10):1186-96.

Comparison 2e: Doses of misoprostol in combination regimens (mifepristone plus misoprostol): 400 µg compared with 800 µg vaginal misoprostol

Summary of Findings table for Comparison 2e

Outcome	Anticipated absolute effect * (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comment
	Risk with 800 µg vaginal misoprostol	Risk with 400 µg vaginal misoprostol				
Efficacy: ongoing pregnancy	11 per 1000	**24 per 1000** (11–55)	**RR 2.23** (0.98–5.11)	1482 (1 RCT) [1]	⊕⊕⊕◯ MODERATE [a]	There is probably no difference in this outcome when a dose of 400 µg versus 800 µg misoprostol is used vaginally
Efficacy: completed without surgical intervention	945 per 1000	**917 per 1000** (850–992)	**RR 0.97** (0.90–1.05)	1482 (1 RCT) [1]	⊕⊕⊕◯ MODERATE [a]	There is probably no difference in this outcome when a dose of 400 µg versus 800 µg misoprostol is used vaginally
Efficacy: expulsion time	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies)	—	No direct evidence identified
Safety: serious adverse events and complications, such as hospitalization, blood transfusion, need for further surgery beyond interventions to complete the removal of products, or death	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies) [b]	—	No direct evidence identified
Side-effects: bleeding	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies) [b]	—	No direct evidence identified
Side-effects: pain	981 per 1000	**972 per 1000** (903–1000)	**RR 0.99** (0.92–1.07)	1499 (1 RCT) [1]	⊕⊕◯◯ LOW [a,c]	Our confidence in the direct estimate is limited; the true effect may be substantially different from the estimate of the effect
Side-effects: vomiting	169 per 1000	**142 per 1000** (112–183)	**RR 0.84** (0.66–1.08)	1499 (1 RCT) [1]	⊕⊕◯◯ LOW [a,c]	Our confidence in the direct estimate is limited; the true effect may be substantially different from the estimate of the effect

Outcome	Anticipated absolute effect * (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comment
	Risk with 800 µg vaginal misoprostol	Risk with 400 µg vaginal misoprostol				
Satisfaction	946 per 1000	**937 per 1000** (870–1000)	**RR 0.99** (0.92–1.07)	1479 (1 RCT) [1,d]	⨁⨁◯◯ LOW [a,c]	Our confidence in the direct estimate is limited; the true effect may be substantially different from the estimate of the effect

CI: confidence interval; RCT: randomized controlled trial; RR: risk ratio

* The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect is close to the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Downgraded one level: results from only one trial.
b. Data not disaggregated by this comparison.
c. Subject to recall and/or courtesy bias.
d. Answered "highly satisfied".

References

1. von Hertzen H, Huong NT, Piaggio G, Bayalag M, Cabezas E, Fang AH, et al. Misoprostol dose and route after mifepristone for early medical abortion: a randomised controlled noninferiority trial. BJOG. 2010;117(10):1186-96.

Comparison 2f: Doses of misoprostol in combination regimens (mifepristone plus misoprostol): 400 µg compared with 600 µg oral misoprostol

Summary of Findings table for Comparison 2f

Outcome	Anticipated absolute effect * (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comment
	Risk with 600 µg oral misoprostol	Risk with 400 µg oral misoprostol				
Efficacy: ongoing pregnancy	3 per 1000	**1 per 1000** (0–25)	**RR 0.33** (0.01–8.10)	638 (1 RCT) [1]	⊕⊕◯◯ LOW [a,b]	Our confidence in the direct estimate is limited; the true effect may be substantially different from the estimate of the effect
Efficacy: completed without surgical intervention	928 per 1000	**937 per 1000** (844–1000)	**RR 1.01** (0.91–1.13)	638 (1 RCT) [1]	⊕⊕◯◯ LOW [a,b]	Our confidence in the direct estimate is limited; the true effect may be substantially different from the estimate of the effect
Efficacy: expulsion time	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies)	—	No direct evidence identified
Safety: serious adverse events and complications, such as hospitalization, blood transfusion, need for further surgery beyond interventions to complete the removal of products, or death	3 per 1000	**1 per 1000** (0–25)	**RR 0.33** (0.01–8.10)	638 (1 RCT) [1,c]	⊕⊕◯◯ LOW [a,b]	Our confidence in the direct estimate is limited; the true effect may be substantially different from the estimate of the effect
Side-effects: bleeding	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies)	—	No direct evidence identified
Side-effects: pain	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies)	—	No direct evidence identified
Side-effects: vomiting	236 per 1000	**200 per 1000** (146–271)	**RR 0.85** (0.62–1.15)	637 (1 RCT) [1]	⊕⊕◯◯ LOW [a,b]	Our confidence in the direct estimate is limited; the true effect may be substantially different from the estimate of the effect

Outcome	Anticipated absolute effect * (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comment
	Risk with 600 µg oral misoprostol	Risk with 400 µg oral misoprostol				
Satisfaction	881 per 1000	**899 per 1000** (802–1000)	**RR 1.02** (0.91–1.16)	599 (1 RCT) [1]	⊕⊕◯◯ LOW [b,d]	Our confidence in the direct estimate is limited; the true effect may be substantially different from the estimate of the effect

CI: confidence interval; RCT: randomized controlled trial; RR: risk ratio
* The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect is close to the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Both studies unblinded (providers, participants and outcome assessors). Risk of selection bias with unclear allocation concealment.
b. Downgraded one level for inconsistency as only one trial included.
c. Blood transfusion.
d. Subject to recall and courtesy bias.

Reference

1. Shannon C, Wiebe E, Jacot F, Guilbert E, Dunn S, Sheldon WR, et al. Regimens of misoprostol with mifepristone for early medical abortion: a randomised trial. BJOG. 2006;113(6):621-8.

Comparison 2g: Doses of misoprostol in combination regimens (mifepristone plus misoprostol): excluded studies

The systematic review of the literature identified three studies that could not be included into the Summary of Findings table for this comparison. The first, by Creinin et al. *(1)* was excluded for using a non-standard dose of mifepristone. A second study, by Chen et al. *(2)*, was excluded for not reporting on the primary outcome. And a third study, by Tsai et al. *(3)*, was excluded because it did not state how the misoprostol was administered.

References

1. Creinin MD, Schwartz JL, Pymar HC, Fink W. Efficacy of mifepristone followed on the same day by misoprostol for early termination of pregnancy: report of a randomised trial. BJOG. 2001;108(5):469-73.
2. Chen QJ, Zhang J, Huang ZR, Fan XF, Wang HY, Zhu H, et al. Mifepristone in combination with misoprostol for the termination of pregnancy at 8–16 weeks' gestational age: a multicentre randomized controlled trial. J Reprod Contracept. 2013;24(2):101-13.
3. Tsai EM, Yang CH, Lee JN. Medical abortion with mifepristone and misoprostol: a clinical trial in Taiwanese women. J Formos Med Assoc. 2002;101(4):277-82.

Comparison 3a: Dosing intervals in combination regimens (mifepristone plus misoprostol): 800 µg vaginal misoprostol < 8 hours compared with > 24 hours after mifepristone

Summary of Findings table for Comparison 3a

Outcome	Anticipated absolute effect* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comment
	Risk with 800 µg vaginal misoprostol given > 24 h after 200 mg mifepristone	Risk with 800 µg vaginal misoprostol given < 8 h after 200 mg mifepristone				
Efficacy: ongoing pregnancy	5 per 1000	**12 per 1000** (4–38)	**RR 2.23** (0.69–7.20)	1525 (2 RCTs) [1,2]	⊕⊕⊕◯ MODERATE [a]	800 µg misoprostol vaginally administered within 8 h compared with after 24 h probably does not affect this outcome
Efficacy: completed without surgical intervention	967 per 1000	**948 per 1000** (880–1000)	**RR 0.98** (0.91–1.06)	1525 (2 RCTs) [1,2]	⊕⊕⊕◯ MODERATE [a]	800 µg misoprostol vaginally administered within 8 h compared with after 24 h probably does not affect this outcome
Efficacy: expulsion time	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies)	—	No direct evidence identified
Safety: serious adverse events and complications, such as hospitalization, blood transfusion, need for further surgery beyond interventions to complete the removal of products, or death	0 per 1000	**0 per 1000** (0–0)	**RR 0.99** (0.02–49.60)	1100 (1 RCT) [1]	⊕⊕⊕◯ MODERATE [b]	800 µg misoprostol vaginally administered within 8 h compared with after 24 h probably does not affect this outcome
Side-effects: bleeding	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies) [c]	—	No direct evidence identified
Side-effects: pain	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies) [c]	—	No direct evidence identified

Outcome	Anticipated absolute effect * (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comment
	Risk with 800 µg vaginal misoprostol given > 24 h after 200 mg mifepristone	Risk with 800 µg vaginal misoprostol given < 8 h after 200 mg mifepristone				
Side-effects: vomiting	272 per 1000	**283 per 1000** (236–337)	**RR 1.04** (0.87–1.24)	1446 (2 RCTs) [1,2]	⊕⊕⊕◯ MODERATE [d]	800 µg misoprostol vaginally administered within 8 h compared with after 24 h probably does not affect this outcome
Satisfaction	977 per 1000	**996 per 1000** (850–1000)	**RR 1.02** (0.87–1.18)	357 (1 RCT) [2]	⊕⊕◯◯ LOW [b,d]	Our confidence in the direct estimate is limited; the true effect may be substantially different from the estimate of the effect

CI: confidence interval; RCT: randomized controlled trial; RR: risk ratio
* The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect is close to the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Explanations
a. Downgraded one level: outcome assessed differently across studies, in terms of both how and when it was measured.
b. Downgraded one level for inconsistency: only one trial included.
c. Creinin et al. *(1)* reported no significant difference in the experience of bleeding or pain between groups. A score on a visual analogue scale (VAS) was used, which could not be entered into GRADE.
d. Downgraded one level: data self-reported and subject to recall bias.

References

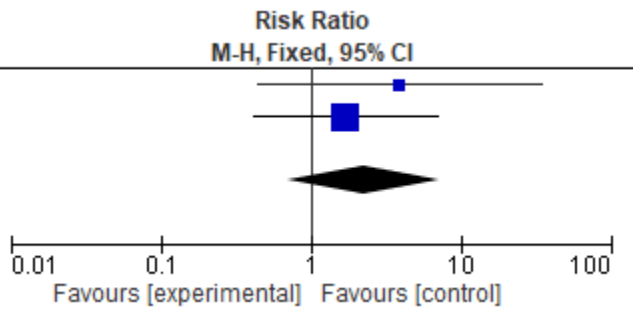
1. Creinin MD, Schreiber CA, Bednarek P, Lintu H, Wagner MS, Meyn LA. Mifepristone and misoprostol administered simultaneously versus 24 hours apart for abortion: a randomized controlled trial. Obstet Gynecol. 2007;109(4):885-94.
2. Guest J, Chien PF, Thomson MA, Kosseim ML. Randomised controlled trial comparing the efficacy of same-day administration of mifepristone and misoprostol for termination of pregnancy with the standard 36 to 48 hour protocol. BJOG. 2007;114(2):207-15.

Forest plots for Comparison 3a

Analysis 1. Efficacy: ongoing pregnancy

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Creinin 2007	4	554	1	546	25.4%	3.94 [0.44, 35.16]
Guest 2007	5	210	3	215	74.6%	1.71 [0.41, 7.05]
Total (95% CI)		**764**		**761**	**100.0%**	**2.27 [0.70, 7.35]**
Total events	9		4			

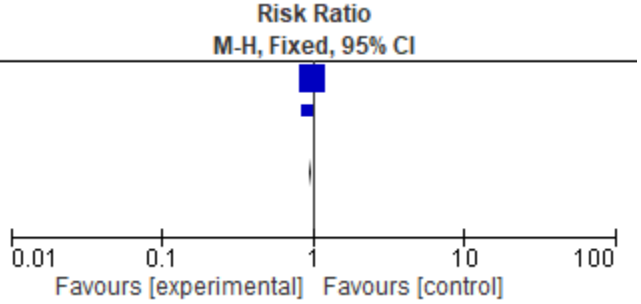
Heterogeneity: Chi² = 0.40, df = 1 (P = 0.53); I² = 0%
Test for overall effect: Z = 1.37 (P = 0.17)



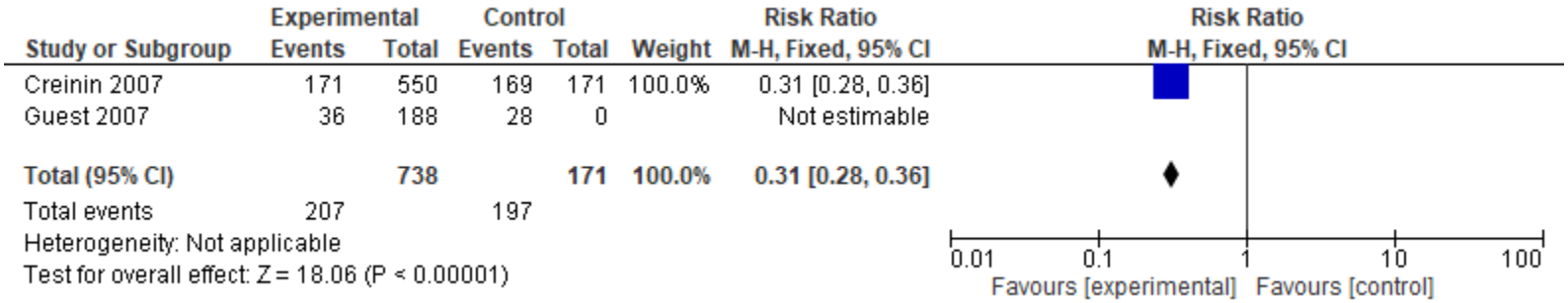
Analysis 2. Efficacy: completed without surgical intervention

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Creinin 2007	527	554	529	549	72.2%	0.99 [0.96, 1.01]
Guest 2007	187	210	207	215	27.8%	0.92 [0.88, 0.98]
Total (95% CI)		**764**		**764**	**100.0%**	**0.97 [0.95, 0.99]**
Total events	714		736			

Heterogeneity: Chi² = 4.89, df = 1 (P = 0.03); I² = 80%
Test for overall effect: Z = 2.56 (P = 0.01)



Analysis 3. Side-effects: vomiting



Comparison 3b: Dosing intervals in combination regimens (mifepristone plus misoprostol): 400–800 µg vaginal misoprostol given 24 hours compared with 48 hours after mifepristone

Summary of Findings table for Comparison 3b

Outcome	Anticipated absolute effect* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comment
	Risk with 400–800 µg vaginal misoprostol given 48 h after mifepristone	Risk with 400–800 µg vaginal misoprostol given 24 h after mifepristone				
Efficacy: ongoing pregnancy	8 per 1000	**7 per 1000** (3–16)	**RR 0.92** (0.40–2.12)	3301 (3 RCTs) [1–3]	⊕◯◯◯ VERY LOW [a,b]	We are uncertain about the effect on this outcome because the certainty of the evidence is very low
Efficacy: completed without surgical intervention	940 per 1000	**931 per 1000** (752–1000)	**RR 0.99** (0.80–1.23)	192 (3 RCTs) [1–3]	⊕◯◯◯ VERY LOW [a,b]	We are uncertain about the effect on this outcome because the certainty of the evidence is very low
Efficacy: expulsion time	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies)	—	No direct evidence identified
Safety: serious adverse events and complications, such as hospitalization, blood transfusion, need for further surgery beyond interventions to complete the removal of products, or death	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies)	—	No direct evidence identified
Side-effects: bleeding	23 per 1000	**22 per 1000** (3–154)	**RR 0.98** (0.14–6.79)	178 (1 RCT) [1,c]	⊕◯◯◯ VERY LOW [a,b]	We are uncertain about the effect on this outcome because the certainty of the evidence is very low
Side-effects: pain	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies)	—	No direct evidence identified

Outcome	Anticipated absolute effect * (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comment
	Risk with 400–800 µg vaginal misoprostol given 48 h after mifepristone	Risk with 400–800 µg vaginal misoprostol given 24 h after mifepristone				
Side-effects: vomiting	211 per 1000	**195 per 1000** (169–220)	**RR 0.92** (0.80–1.04)	344 (3 RCTs) [1–3]	⊕◯◯◯ VERY LOW [a,b]	We are uncertain about the effect on this outcome because the certainty of the evidence is very low
Satisfaction	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies)	—	No direct evidence identified

CI: confidence interval; RCT: randomized controlled trial; RR: risk ratio

* The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect is close to the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Allocation concealment not specified. Study unblinded to outcome assessors.
b. Misoprostol dose ranged from 400–800 µg.
c. Defined in the study *(1)* as bleeding that warranted a surgical intervention.

References

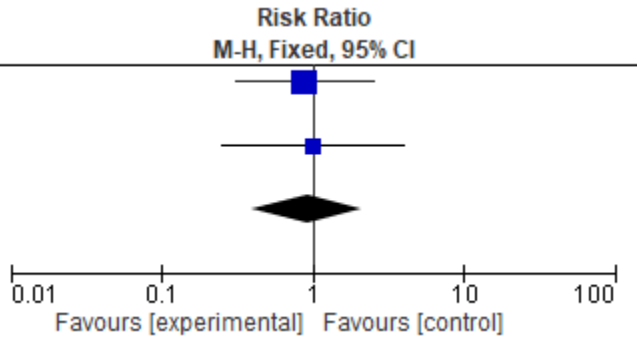
1. Verma ML, Singh U, Singh N, Shankhwar P, Srivastava D. Efficacy of misoprostol administration 24 hours after mifepristone for termination of early pregnancy. Indian J Med Sci. 2011;65(12):511-7.
2. Schaff EA, Fielding SL, Westhoff C, Ellertson C, Eisinger SH, Stadalius LS, et al. Vaginal misoprostol administered 1, 2, or 3 days after mifepristone for early medical abortion: a randomized trial. JAMA. 2000;284(15):1948-53.
3. von Hertzen H, Piaggio G, Wojdyla D, Marions L, My Huong N, Tang O, et al. Two mifepristone doses and two intervals of misoprostol administration for termination of early pregnancy: a randomised factorial controlled equivalence trial. BJOG. 2009;116:381-9.

Forest plots for Comparison 3b

Analysis 1. Efficacy: ongoing pregnancy

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Schaff 2000	5	704	11	1354	65.3%	0.87 [0.30, 2.51]
Verma 2011	0	92	0	88		Not estimable
Von Hertzen 2008	4	531	4	532	34.7%	1.00 [0.25, 3.99]
Total (95% CI)		**1327**		**1974**	**100.0%**	**0.92 [0.40, 2.12]**
Total events	9		15			

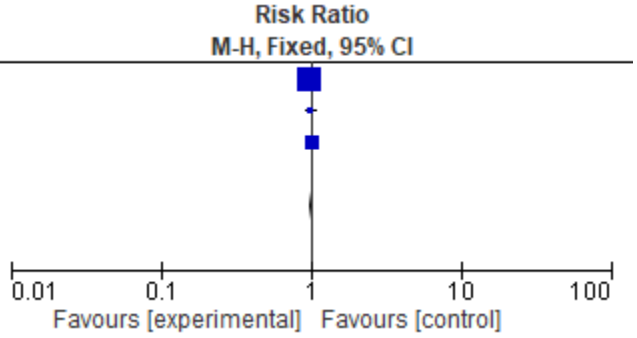
Heterogeneity: Chi² = 0.02, df = 1 (P = 0.88); I² = 0%
Test for overall effect: Z = 0.20 (P = 0.84)



Analysis 2. Efficacy: completed without surgical intervention

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Schaff 2000	689	704	1347	1354	61.5%	0.98 [0.97, 1.00]
Verma 2011	86	92	83	88	5.7%	0.99 [0.92, 1.07]
Von Hertzen 2008	499	531	492	532	32.8%	1.02 [0.98, 1.05]
Total (95% CI)		**1327**		**1974**	**100.0%**	**0.99 [0.98, 1.01]**
Total events	1274		1922			

Heterogeneity: Chi² = 5.23, df = 2 (P = 0.07); I² = 62%
Test for overall effect: Z = 0.75 (P = 0.45)

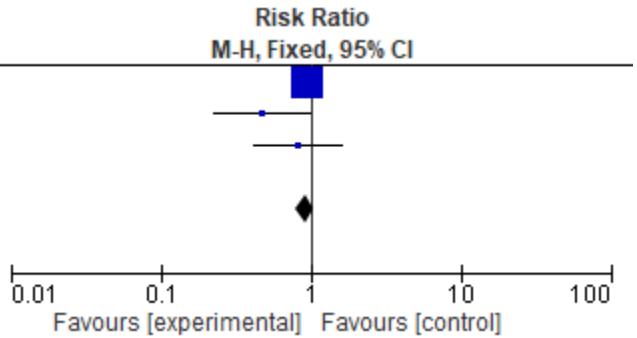


Analysis 3. Side-effects: vomiting

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Schaff 2000	218	704	442	1354	89.1%	0.95 [0.83, 1.08]
Verma 2011	9	100	19	100	5.6%	0.47 [0.23, 1.00]
Von Hertzen 2008	15	526	18	521	5.3%	0.83 [0.42, 1.62]
Total (95% CI)		**1330**		**1975**	**100.0%**	**0.92 [0.80, 1.04]**
Total events	242		479			

Heterogeneity: $Chi^2 = 3.38$, df = 2 (P = 0.18); $I^2 = 41\%$

Test for overall effect: Z = 1.33 (P = 0.18)



Comparison 3c: Dosing intervals in combination regimens (mifepristone plus misoprostol): 400 µg vaginal misoprostol given concurrently compared with 24 hours after 200 mg mifepristone

Summary of Findings table for Comparison 3c

Outcome	Anticipated absolute effect* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comment
	Risk with 400 µg vaginal misoprostol given 24 h after 200 mg mifepristone	Risk with 400 µg vaginal misoprostol given concurrently with 200 mg mifepristone				
Efficacy: ongoing pregnancy	0 per 1000	**0 per 1000** (0–0)	**RR 0.98** (0.02–49.25)	258 (2 RCTs) [1,2]	⨁◯◯◯ VERY LOW [a–c]	We are uncertain about the effect on this outcome because the certainty of the evidence is very low
Efficacy: completed without surgical intervention	957 per 1000	**967 per 1000** (804–1000)	**RR 1.01** (0.84–1.21)	280 (2 RCTs) [1,2]	⨁◯◯◯ VERY LOW [a,c,d]	We are uncertain about the effect on this outcome because the certainty of the evidence is very low
Efficacy: expulsion time	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies) [e]	—	No direct evidence identified
Safety: serious adverse events and complications, such as hospitalization, blood transfusion, need for further surgery beyond interventions to complete the removal of products, or death	0 per 1000	**0 per 1000** (0–0)	**RR 1.00** (0.02–50.01)	178 (2 RCTs) [1,2]	⨁◯◯◯ VERY LOW [a,c,d]	We are uncertain about the effect on this outcome because the certainty of the evidence is very low
Side-effects: bleeding	23 per 1000	**22 per 1000** (3–154)	**RR 0.98** (0.14–6.79)	178 (1 RCT) [1,f]	⨁◯◯◯ VERY LOW [a,c,g]	We are uncertain about the effect on this outcome because the certainty of the evidence is very low
Side-effects: pain	50 per 1000	**74 per 1000** (13–417)	**RR 1.47** (0.25–8.33)	80 (1 RCT) [2,h]	⨁◯◯◯ VERY LOW [a,c,g]	We are uncertain about the effect on this outcome because the certainty of the evidence is very low

Outcome	Anticipated absolute effect * (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comment
	Risk with 400 µg vaginal misoprostol given 24 h after 200 mg mifepristone	Risk with 400 µg vaginal misoprostol given concurrently with 200 mg mifepristone				
Side-effects: vomiting	141 per 1000	**110 per 1000** (58–214)	**RR 0.78** (0.41–1.52)	258 (2 RCTs) [1,2]	⊕◯◯◯ VERY LOW [a,c]	We are uncertain about the effect on this outcome because the certainty of the evidence is very low
Satisfaction	950 per 1000	**969 per 1000** (703–1000)	**RR 1.02** (0.74–1.39)	80 (1 RCT) [2]	⊕◯◯◯ VERY LOW [a,c,d]	We are uncertain about the effect on this outcome because the certainty of the evidence is very low

CI: confidence interval; RCT: randomized controlled trial; RR: risk ratio
* The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect is close to the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Downgraded for high risk of reporting and detection biases (Goel et al. *[2]*). Reporting bias: outcome of time to expulsion not reported although it was stated as an outcome. High risk for selection bias with unclear randomization and allocation (Verma et al. *[1]*).
b. Misoprostol administered at 24 or 48 hours in the comparison arm.
c. Downgraded one level in imprecision: small numbers and broad 95% CI.
d. Results not separated by number of doses of misoprostol received by women in the comparison arm.
e. Goel et al. *(2)* reported an expulsion time of 6.5 + 1.48 hours in the intervention arm, compared with 5.95 + 1.81 hours in the comparison arm.
f. Defined in the study *(1)* as heavy enough to warrant a surgical intervention.
g. Downgraded one level: results from only one trial.
h. Defined in the study *(2)* as "intolerable abdominal pain".

References

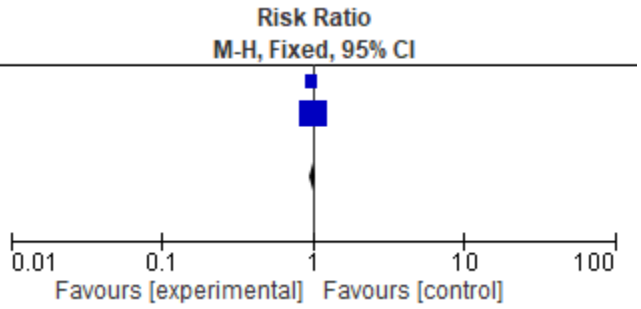
1. Verma ML, Singh U, Singh N, Sankhwar PL, Qureshi S. Efficacy of concurrent administration of mifepristone and misoprostol for termination of pregnancy. Hum Fertil. 2017;20(1):43-7.
2. Goel A, Mittal S, Taneja BK, Singal N, Attri S. Simultaneous administration of mifepristone and misoprostol for early termination of pregnancy: a randomized controlled trial. Arch Gynecol Obstet. 2011;283(6):1409-13.

Forest plots for Comparison 3c

Analysis 1. Efficacy: completed without surgical intervention

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Goel 2011	38	40	39	40	29.1%	0.97 [0.89, 1.06]
Verma 2017	96	100	95	100	70.9%	1.01 [0.95, 1.07]
Total (95% CI)		**140**		**140**	**100.0%**	**1.00 [0.95, 1.05]**
Total events	134		134			

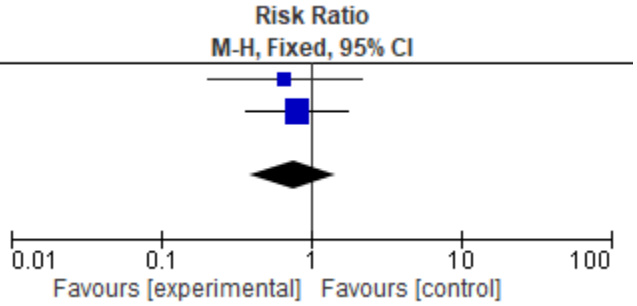
Heterogeneity: Chi² = 0.46, df = 1 (P = 0.50); I² = 0%
Test for overall effect: Z = 0.00 (P = 1.00)



Analysis 2. Side-effects: vomiting

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Goel 2011	4	40	6	40	33.1%	0.67 [0.20, 2.18]
Verma 2017	10	90	12	88	66.9%	0.81 [0.37, 1.79]
Total (95% CI)		**130**		**128**	**100.0%**	**0.77 [0.40, 1.47]**
Total events	14		18			

Heterogeneity: Chi² = 0.08, df = 1 (P = 0.78); I² = 0%
Test for overall effect: Z = 0.80 (P = 0.42)



Comparison 3d: Dosing intervals in combination regimens (mifepristone plus misoprostol): 400 µg oral misoprostol given < 8 hours after 600 mg mifepristone compared with 400 µg oral misoprostol given 48 hours after 200 mg mifepristone

Summary of Findings table for Comparison 3d

Outcome	Anticipated absolute effect* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comment
	Risk with 400 µg oral misoprostol given 48 h after 200 mg mifepristone	Risk with 400 µg oral misoprostol given < 8 h after 600 mg mifepristone				
Efficacy: ongoing pregnancy	0 per 1000	**0 per 1000** (0–0)	**RR 8.34** (0.46–151.20)	100 (1 RCT) [1]	⊕◯◯◯ VERY LOW [a,b]	We are uncertain about the effect on this outcome because the certainty of the evidence is very low
Efficacy: completed without surgical intervention	900 per 1000	**819 per 1000** (594–1000)	**RR 0.91** (0.66–1.25)	100 (1 RCT) [1]	⊕◯◯◯ VERY LOW [a,b]	We are uncertain about the effect on this outcome because the certainty of the evidence is very low
Efficacy: expulsion time	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies)	—	No direct evidence identified
Safety: serious adverse events and complications, such as hospitalization, blood transfusion, need for further surgery beyond interventions to complete the removal of products, or death	20 per 1000	**39 per 1000** (4–418)	**RR 1.96** (0.18–20.90)	100 (1 RCT) [1,c]	⊕◯◯◯ VERY LOW [a,b]	We are uncertain about the effect on this outcome because the certainty of the evidence is very low
Side-effects: bleeding	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies) [d]	—	No direct evidence identified
Side-effects: pain	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies)	—	No direct evidence identified

Outcome	Anticipated absolute effect* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comment
	Risk with 400 µg oral misoprostol given 48 h after 200 mg mifepristone	Risk with 400 µg oral misoprostol given < 8 h after 600 mg mifepristone				
Side-effects: vomiting	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies)	—	No direct evidence identified
Satisfaction	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies)	—	No direct evidence identified

CI: confidence interval; RCT: randomized controlled trial; RR: risk ratio
* The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect is close to the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Downgraded one level for inconsistency: only one trial included.
b. Downgraded two levels for imprecision: few events and broad 95% CI.
c. Serious adverse events were defined by Tendler et al. *(1)* as "other complications".
d. Creinin et al. *(2)* reported no significant difference in experience of bleeding or pain between groups. A score on a visual analogue scale (VAS) score was used, which could not be entered into GRADE.
e. Downgraded one level: data self-reported and subject to recall bias.

References

1. Tendler R, Bornstein J, Kais M, Masri I, Odeh M. Early versus late misoprostol administration after mifepristone for medical abortion. Arch Gynecol Obstet. 2015;292(5):1051-4.
2. Excluded (does not report on our primary outcome): Creinin MD, Pymar HC, Schwartz JL. Mifepristone 100 mg in abortion regimens. Obstet Gynecol. 2001;98(3):434-9.

Comparison 4a: Routes of misoprostol administration in combination regimens (mifepristone plus misoprostol): 400 µg misoprostol administered sublingually compared with vaginally

Summary of Findings table for Comparison 4a

Outcome	Anticipated absolute effect* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comment
	Risk with 400 µg vaginal misoprostol	Risk with 400 µg sublingual misoprostol				
Efficacy: ongoing pregnancy	24 per 1000	**19 per 1000** (10–38)	**RR 0.79** (0.39–1.55)	1479 (1 RCT) [1]	⊕⊕⊕◯ MODERATE [a]	There is probably no difference in ongoing pregnancy rates when 400 µg misoprostol is administered vaginally versus sublingually
Efficacy: completed without surgical intervention	896 per 1000	**905 per 1000** (842–976)	**RR 1.01** (0.94–1.09)	1479 (1 RCT) [1]	⊕⊕⊕◯ MODERATE [a]	There is probably no difference in the need for surgery to complete the abortion when 400 µg misoprostol is administered vaginally versus sublingually
Efficacy: expulsion time	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies)	—	No direct evidence identified
Safety: serious adverse events and complications, such as hospitalization, blood transfusion, need for further surgery beyond interventions to complete the removal of products, or death	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies)	—	There is probably no difference in serious adverse events when 400 µg misoprostol is administered vaginally versus sublingually
Side-effects: bleeding	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies)	—	No direct evidence identified
Side-effects: pain	960 per 1000	**970 per 1000** (893–1000)	**RR 1.01** (0.93–1.08)	1499 (1 RCT) [1]	⊕⊕⊕◯ MODERATE [b]	There is probably no difference in pain when 400 µg misoprostol is administered vaginally versus sublingually

Outcome	Anticipated absolute effect * (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comment
	Risk with 400 µg vaginal misoprostol	Risk with 400 µg sublingual misoprostol				
Side-effects: vomiting	140 per 1000	**185 per 1000** (147–234)	**RR 1.32** (1.05–1.67)	1499 (1 RCT) [1]	⊕⊕⊕◯ MODERATE [b]	There is probably no difference in emesis when 400 µg misoprostol is administered vaginally versus sublingually
Satisfaction	936 per 1000	**936 per 1000** (880–1000)	**RR 1.00** (0.94–1.07)	1473 (1 RCT) [1]	⊕⊕⊕◯ MODERATE [b]	There is probably no difference in satisfaction when 400 µg misoprostol is administered vaginally versus sublingually

CI: confidence interval; RCT: randomized controlled trial; RR: risk ratio
* The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect is close to the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Administration not blinded. Uncertain if outcome assessment was blinded.
b. Self-reported data subject to recall and courtesy biases.

Reference

1. von Hertzen H, Huong NT, Piaggio G, Bayalag M, Cabezas E, Fang AH, et al. Misoprostol dose and route after mifepristone for early medical abortion: a randomised controlled noninferiority trial. BJOG. 2010;117(10):1186-96.

Comparison 4b: Routes of misoprostol administration in combination regimens (mifepristone plus misoprostol): 600/800 µg misoprostol administered sublingually compared with 800 µg administered vaginally

Summary of Findings table for Comparison 4b

Outcome	Anticipated absolute effect* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comment
	Risk with 800 µg vaginal misoprostol	Risk with 600/800 µg sublingual misoprostol				
Efficacy: ongoing pregnancy	17 per 1000	**2 per 1000** (1–51)	**RR 0.15** (0.08–3.05)	346 (2 RCTs) [1,2]	⊕⊕◯◯ LOW [a,b]	Our confidence in the direct estimate is limited; the true effect may be substantially different from the estimate of the effect
Efficacy: completed without surgical intervention	956 per 1000	**965 per 1000** (832–1000)	**RR 1.01** (0.87–1.18)	346 (2 RCTs) [1,2]	⊕⊕◯◯ LOW [a,b]	Our confidence in the direct estimate is limited; the true effect may be substantially different from the estimate of the effect
Efficacy: expulsion time	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies) [c]	—	No direct evidence identified
Safety: serious adverse events and complications, such as hospitalization, blood transfusion, need for further surgery beyond interventions to complete the removal of products, or death	0 per 1000	**0 per 1000** (0–0)	**RR 1.00** (0.02–49.96)	224 (1 RCT) [1]	⊕⊕◯◯ LOW [b,d,e]	Our confidence in the direct estimate is limited; the true effect may be substantially different from the estimate of the effect
Side-effects: bleeding	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies) [f]	—	No direct evidence identified
Side-effects: pain	964 per 1000	**974 per 1000** (810–1000)	**RR 1.01** (0.84–1.22)	224 (1 RCT) [1]	⊕⊕⊕◯ MODERATE [g]	There is probably no difference in pain when 600/800 µg misoprostol is administered sublingually compared with 800 µg misoprostol administered vaginally

Outcome	Anticipated absolute effect* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comment
	Risk with 800 µg vaginal misoprostol	Risk with 600/800 µg sublingual misoprostol				
Side-effects: vomiting	964 per 1000	**521 per 1000** (386–704)	**RR 0.54** (0.40–0.73)	224 (1 RCT) [1]	⊕⊕⊕◯ MODERATE [g]	There is probably no difference in emesis when 600/800 µg misoprostol is administered sublingually compared with 800 µg misoprostol administered vaginally
Satisfaction	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies)	—	No direct evidence identified

CI: confidence interval; RCT: randomized controlled trial; RR: risk ratio
* The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect is close to the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Hamoda et al. *(2)* used a sublingual dose of 600 µg misoprostol while Tang et al. *(1)* used a sublingual dose of 800 µg.
b. Downgraded one level for imprecision: few events and broad 95% CI.
c. Tang et al. *(1)* reported a mean expulsion time of 3.65 hours (1–88) for the intervention versus 3.95 hours (2–101) for the comparison group.
d. Downgraded one level for inconsistency: only one trial included.
e. Did not explicitly define serious adverse events.
f. Tang et al. *(1)* reported a mean of 17 days of bleeding for both groups.
g. Self-reported data subject to recall and courtesy biases.

References

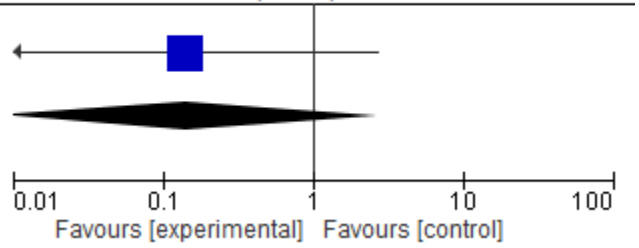
1. Tang OS, Chan CC, Ng EH, Lee SW, Ho PC. A prospective, randomized, placebo-controlled trial on the use of mifepristone with sublingual or vaginal misoprostol for medical abortions of less than 9 weeks gestation. Hum Reprod. 2003;18(11):2315-8.
2. Hamoda H, Ashok PW, Flett GM, Templeton A. A randomised controlled trial of mifepristone in combination with misoprostol administered sublingually or vaginally for medical abortion up to 13 weeks of gestation. BJOG. 2005;112(8):1102-8.

Forest plots for Comparison 4b

Analysis 1. Efficacy: ongoing pregnancy

	Experimental		Control			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Hamoda 2005	0	53	0	69		Not estimable	
Tang 2003	0	112	3	112	100.0%	0.14 [0.01, 2.73]	
Total (95% CI)		**165**		**181**	**100.0%**	**0.14 [0.01, 2.73]**	
Total events	0		3				

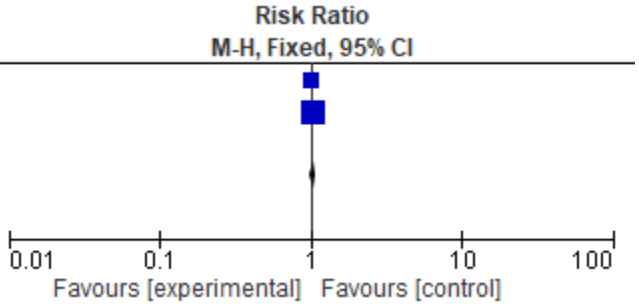
Heterogeneity: Not applicable
Test for overall effect: Z = 1.29 (P = 0.20)



Analysis 2. Efficacy: completed without surgical intervention

	Experimental		Control			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Hamoda 2005	53	53	68	69	36.2%	1.01 [0.97, 1.06]	
Tang 2003	110	112	105	112	63.8%	1.05 [0.99, 1.11]	
Total (95% CI)		**165**		**181**	**100.0%**	**1.03 [1.00, 1.07]**	
Total events	163		173				

Heterogeneity: $Chi^2 = 1.19$, df = 1 (P = 0.28); $I^2 = 16\%$
Test for overall effect: Z = 1.77 (P = 0.08)



Comparison 4c: Routes of misoprostol administration in combination regimens (mifepristone plus misoprostol): 800 µg misoprostol administered vaginally compared with sublingually

Summary of Findings table for Comparison 4c

Outcome	Anticipated absolute effect * (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comment
	Risk with 800 µg sublingual misoprostol	Risk with 800 µg vaginal misoprostol				
Efficacy: ongoing pregnancy	11 per 1000	**5 per 1000** (2–18)	**RR 0.50** (0.15–1.67)	1483 (1 RCT) [1]	⊕⊕⊕◯ MODERATE [a]	There is probably no difference in this outcome when 800 µg misoprostol is administered vaginally versus sublingually
Efficacy: completed without surgical intervention	945 per 1000	**935 per 1000** (869–1000)	**RR 0.99** (0.92–1.07)	1483 (1 RCT) [1]	⊕⊕⊕◯ MODERATE [a]	There is probably no difference in this outcome when 800 µg misoprostol is administered vaginally versus sublingually
Efficacy: expulsion time	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies)	—	No direct evidence identified
Safety: serious adverse events and complications, such as hospitalization, blood transfusion, need for further surgery beyond interventions to complete the removal of products, or death	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies) [b]	—	No direct evidence identified
Side-effects: bleeding	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies)	—	No direct evidence identified
Side-effects: pain	981 per 1000	**981 per 1000** (913–1000)	**RR 1.00** (0.93–1.07)	1501 (2 RCTs) [2,3]	⊕⊕◯◯ LOW [a,c]	Our confidence in the direct estimate is limited; the true effect may be substantially different from the estimate of the effect

Outcome	Anticipated absolute effect * (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comment
	Risk with 800 µg sublingual misoprostol	Risk with 800 µg vaginal misoprostol				
Side-effects: vomiting	169 per 1000	**237 per 1000** (193–291)	**RR 1.40** (1.14–1.72)	1501 (1 RCT) [1]	⊕⊕◯◯ LOW [a,c]	Our confidence in the direct estimate is limited; the true effect may be substantially different from the estimate of the effect
Satisfaction	946 per 1000	**937 per 1000** (870–1000)	**RR 0.99** (0.92–1.07)	1481 (1 RCT) [1]	⊕◯◯◯ VERY LOW [a,c]	We are uncertain about the effect on this outcome because the certainty of the evidence is very low

CI: confidence interval; RCT: randomized controlled trial; RR: risk ratio

* The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect is close to the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Downgraded one level: results from only one trial.
b. Data not disaggregated by this comparison.
c. Subject to recall and/or courtesy bias.

Reference

1. von Hertzen H, Huong NT, Piaggio G, Bayalag M, Cabezas E, Fang AH, et al. Misoprostol dose and route after mifepristone for early medical abortion: a randomised controlled noninferiority trial. BJOG. 2010;117(10):1186-96.

Comparison 4d: Routes of misoprostol administration in combination regimens (mifepristone plus misoprostol): 800 µg misoprostol administered orally compared with vaginally

Summary of Findings table for Comparison 4d

Outcome	Anticipated absolute effect* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comment
	Risk with 800 µg vaginal misoprostol	Risk with 800 µg oral misoprostol				
Efficacy: ongoing pregnancy	1 per 1000	**9 per 1000** (3–33)	**RR 6.70** (1.88–23.86)	1287 (3 RCTs) [1–3]	⊕⊕⊕◯ MODERATE [a]	800 µg misoprostol administered orally compared with vaginally probably slightly increases the risk of an ongoing pregnancy
Efficacy: completed without surgical intervention	985 per 1000	**926 per 1000** (837–1000)	**RR 0.94** (0.85–1.04)	1455 (3 RCTs) [1–3]	⊕⊕⊕◯ MODERATE [a]	800 µg misoprostol administered orally compared with vaginally probably does not affect the need for surgical intervention
Efficacy: expulsion time	932 per 1000	**848 per 1000** (699–1000)	**RR 0.91** (0.75–1.10)	263 (1 RCT) [2,b]	⊕◯◯◯ VERY LOW [a,c,d]	We are uncertain about the effect on this outcome because the certainty of the evidence is very low
Safety: serious adverse events and complications, such as hospitalization, blood transfusion, need for further surgery beyond interventions to complete the removal of products, or death	8 per 1000	**3 per 1000** (0–63)	**RR 0.35** (0.01–8.35)	263 (1 RCT) [2]	⊕◯◯◯ VERY LOW [a,c,d]	We are uncertain about the effect on this outcome because the certainty of the evidence is very low
Side-effects: bleeding	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies)	—	No direct evidence identified
Side-effects: pain	2 per 1000	**5 per 1000** (1–52)	**RR 3.25** (0.34–31.15)	1144 (1 RCT) [1]	⊕⊕⊕◯ MODERATE [e]	800 µg misoprostol administered orally compared with vaginally probably does not affect the risk of pain

Outcome	Anticipated absolute effect * (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comment
	Risk with 800 µg vaginal misoprostol	Risk with 800 µg oral misoprostol				
Side-effects: vomiting	356 per 1000	**306 per 1000** (260–363)	**RR 0.86** (0.73–1.02)	1219 (2 RCTs) [1,2]	⨁⨁⨁◯ MODERATE [e]	800 µg misoprostol administered orally compared with vaginally probably does not affect the risk of vomiting
Satisfaction	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies) [f]	—	No direct evidence

CI: confidence interval; RCT: randomized controlled trial; RR: risk ratio

* The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect is close to the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Non-blinding of participants, providers and outcome assessors.
b. el-Refaey et al. *(2)* reported expulsion in less than 4 hours.
c. Downgraded one level for inconsistency: only one trial included.
d. Downgraded one level: few events and wide CI.
e. Downgraded one level: data self-reported and subject to recall bias.
f. Schaff et al. *(1)* reported: "Acceptable to 89% of women in all treatment groups (889/993)".

References

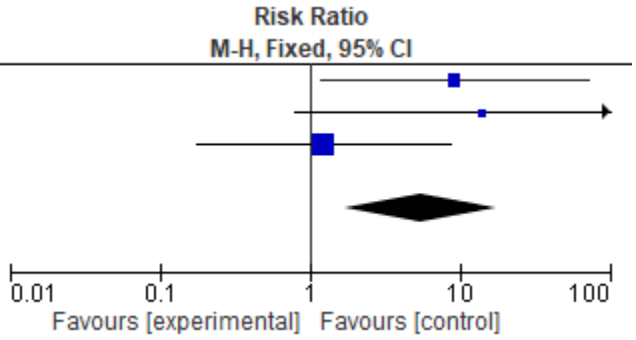
1. Schaff EA, Fielding SL, Westhoff C. Randomized trial of oral versus vaginal misoprostol at one day after mifepristone for early medical abortion. Contraception. 2001;64(2):81-5.
2. el-Refaey H, Rajasekar D, Abdalla M, Calder L, Templeton A. Induction of abortion with mifepristone (RU 486) and oral or vaginal misoprostol. N Engl J Med. 1995;332(15):983-7.
3. Schaff EA, Fielding SL, Westhoff C. Randomized trial of oral versus vaginal misoprostol 2 days after mifepristone 200 mg for abortion up to 63 days of pregnancy Contraception. 2002;66(4):247-50.

Forest plots for Comparison 4d

Analysis 1. Efficacy: ongoing pregnancy

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
El-Refaey 1995	9	130	1	133	30.3%	9.21 [1.18, 71.65]
Schaff 2001	6	548	0	596	14.7%	14.14 [0.80, 250.35]
Schaff 2002	2	219	2	268	55.1%	1.22 [0.17, 8.62]
Total (95% CI)		**897**		**997**	**100.0%**	**5.53 [1.73, 17.69]**
Total events	17		3			

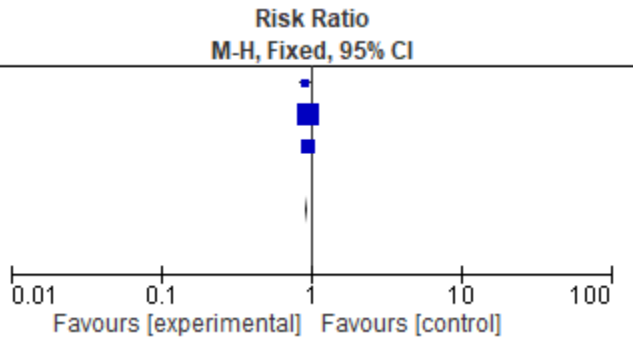
Heterogeneity: Chi² = 2.94, df = 2 (P = 0.23); I² = 32%
Test for overall effect: Z = 2.89 (P = 0.004)



Analysis 2. Efficacy: completed without surgical intervention

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
El-Refaey 1995	113	130	126	133	12.1%	0.92 [0.85, 0.99]
Schaff 2001	519	548	592	596	54.9%	0.95 [0.93, 0.97]
Schaff 2002	246	268	502	522	33.0%	0.95 [0.92, 0.99]
Total (95% CI)		**946**		**1251**	**100.0%**	**0.95 [0.93, 0.97]**
Total events	878		1220			

Heterogeneity: Chi² = 0.97, df = 2 (P = 0.62); I² = 0%
Test for overall effect: Z = 5.15 (P < 0.00001)



Comparison 4e: Routes of misoprostol administration in combination regimens (mifepristone plus misoprostol): 400 µg misoprostol administered orally compared with 800 µg administered vaginally

Summary of Findings table for Comparison 4e

Outcome	Anticipated absolute effect* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comment
	Risk with 800 µg vaginal misoprostol	Risk with 400 µg oral misoprostol				
Efficacy: ongoing pregnancy	2 per 1000	**4 per 1000** (1–26)	**RR 2.38** (0.34–16.81)	1378 (2 RCTs) [1,2]	⊕⊕⊕◯ MODERATE [a]	There is probably no difference in ongoing pregnancy rates when 400 µg misoprostol is given orally versus 800 µg misoprostol given vaginally
Efficacy: completed without surgical intervention	970 per 1000	**951 per 1000** (883–1000)	**RR 0.98** (0.91–1.04)	2025 (2 RCTs) [1,2]	⊕⊕⊕◯ MODERATE [a]	There is probably no difference in need for surgical intervention when 400 µg misoprostol is given orally versus 800 µg misoprostol given vaginally
Efficacy: expulsion time	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies)	—	No direct evidence identified
Safety: serious adverse events and complications, such as hospitalization, blood transfusion, need for further surgery beyond interventions to complete the removal of products, or death	3 per 1000	**1 per 1000** (0–26)	**RR 0.33** (0.01–8.15)	637 (1 RCT) [1,b]	⊕⊕◯◯ LOW [a,c]	Our confidence in the direct estimate is limited; the true effect may be substantially different from the estimate of the effect
Side-effects: bleeding	8 per 1000	**40 per 1000** (12–52)	**RR 5.19** (1.61–6.79)	741 (1 RCT) [2,d]	⊕⊕◯◯ LOW [a,c]	Our confidence in the direct estimate is limited; the true effect may be substantially different from the estimate of the effect
Side-effects: pain	958 per 1000	**900 per 1000** (804–1000)	**RR 0.94** (0.84–1.07)	738 (1 RCT) [2,e]	⊕⊕◯◯ LOW [a,c]	Our confidence in the direct estimate is limited; the true effect may be substantially different from the estimate of the effect

Outcome	Anticipated absolute effect * (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comment
	Risk with 800 µg vaginal misoprostol	Risk with 400 µg oral misoprostol				
Side-effects: vomiting	236 per 1000	**361 per 1000** (252–519)	**RR 1.53** (1.07–2.20)	637 (1 RCT) [1]	⊕⊕◯◯ LOW [a,c]	Our confidence in the direct estimate is limited; the true effect may be substantially different from the estimate of the effect
Satisfaction	881 per 1000	**899 per 1000** (802–1000)	**RR 1.02** (0.91–1.16)	599 (1 RCT) [1,f]	⊕⊕◯◯ LOW [c,g]	Our confidence in the direct estimate is limited; the true effect may be substantially different from the estimate of the effect [f]

CI: confidence interval; RCT: randomized controlled trial; RR: risk ratio

* The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect is close to the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Both studies *(1,2)* unblinded (providers, participants and outcome assessors). Risk of selection bias, with unclear allocation concealment.
b. Shannon et al. *(1)* reported one maternal death due to *C. sordellii* infection.
c. Downgraded one level for inconsistency: only one trial included.
d. Schaff et al. *(2)* defined this as bleeding that warranted a surgical intervention.
e. Shannon et al. *(1)* reported a mean pain score on a visual analogue scale (VAS; 0–10) of 5.8 for the intervention (400 µg oral misoprostol) and 6.7 for the comparator (800 µg vaginal misoprostol).
f. Schaff et al. *(2)* reported that the procedure was "acceptable to 89% of women in all treatment groups" but did not disaggregate by route of administration.
g. Subject to recall and courtesy biases.

References

1. Shannon C, Wiebe E, Jacot F, Guilbert E, Dunn S, Sheldon WR, et al. Regimens of misoprostol with mifepristone for early medical abortion: a randomised trial. BJOG. 2006;113(6):621-8.
2. Schaff EA, Fielding SL, Westhoff C. Randomized trial of oral versus vaginal misoprostol 2 days after mifepristone 200 mg for abortion up to 63 days of pregnancy. Contraception. 2002;66(4):247-50.

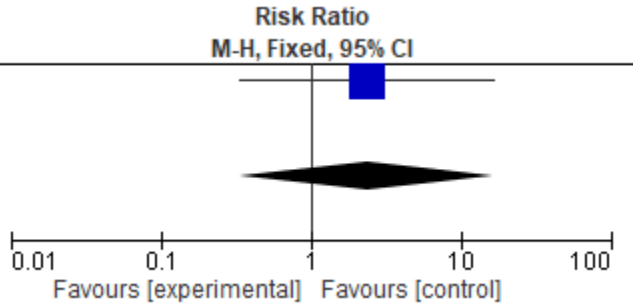
Excluded (did not report on primary outcome): Arvidsson C, Hellborg M, Gemzell-Danielsson K. Preference and acceptability of oral versus vaginal administration of misoprostol in medical abortion with mifepristone. Eur J Obstet Gynecol Reprod Biol. 2005;123(1):87-91.

Forest plots for Comparison 4e

Analysis 1. Efficacy: ongoing pregnancy

	Experimental		Control			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Schaff 2002	2	219	2	522	100.0%	2.38 [0.34, 16.81]
Shannon 2006	0	319	0	318		Not estimable
Total (95% CI)		**538**		**840**	**100.0%**	**2.38 [0.34, 16.81]**
Total events	2		2			

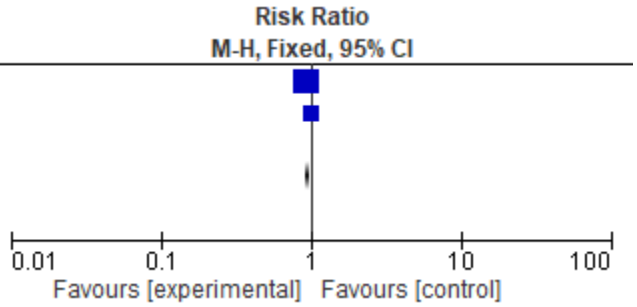
Heterogeneity: Not applicable
Test for overall effect: Z = 0.87 (P = 0.38)



Analysis 2. Efficacy: completed without surgical intervention

	Experimental		Control			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Schaff 2002	371	404	964	984	65.2%	0.94 [0.91, 0.97]
Shannon 2006	302	319	299	318	34.8%	1.01 [0.97, 1.05]
Total (95% CI)		**723**		**1302**	**100.0%**	**0.96 [0.94, 0.98]**
Total events	673		1263			

Heterogeneity: $Chi^2 = 8.32$, df = 1 (P = 0.004); $I^2 = 88\%$
Test for overall effect: Z = 3.23 (P = 0.001)



Comparison 4f: Routes of misoprostol administration in combination regimens (mifepristone plus misoprostol): 800 µg misoprostol administered buccally compared with sublingually

Summary of Findings table for Comparison 4f

Outcome	Anticipated absolute effect* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comment
	Risk with 800 µg sublingual misoprostol	Risk with 800 µg buccal misoprostol				
Efficacy: ongoing pregnancy	22 per 1000	**22 per 1000** (0–1000)	**RR 0.98** (0.02–49.25)	90 (1 RCT) [1]	⊕◯◯◯ VERY LOW [a–c]	We are uncertain about the effect on this outcome because the certainty of the evidence is very low
Efficacy: completed without surgical intervention	978 per 1000	**958 per 1000** (714–1000)	**RR 0.98** (0.73–1.33)	90 (1 RCT) [1]	⊕◯◯◯ VERY LOW [d]	We are uncertain about the effect on this outcome because the certainty of the evidence is very low
Efficacy: expulsion time	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies)	—	No direct evidence identified
Safety: serious adverse events and complications, such as hospitalization, blood transfusion, need for further surgery beyond interventions to complete the removal of products, or death	0 per 1000	**0 per 1000** (0–0)	**RR 0.98** (0.02–48.70)	178 (1 RCT)	⊕◯◯◯ VERY LOW [c,d]	We are uncertain about the effect on this outcome because the certainty of the evidence is very low
Side-effects: bleeding	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies)	—	No direct evidence identified
Side-effects: pain	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies)	—	No direct evidence identified

Outcome	Anticipated absolute effect* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comment
	Risk with 800 µg sublingual misoprostol	Risk with 800 µg buccal misoprostol				
Side-effects: vomiting	141 per 1000	**110 per 1000** (58–214)	**RR 0.78** (0.41–1.52)	258 (1 RCT) [1]	⊕◯◯◯ VERY LOW [c]	We are uncertain about the effect on this outcome because the certainty of the evidence is very low
Satisfaction	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies)	—	No direct evidence identified

CI: confidence interval; RCT: randomized controlled trial; RR: risk ratio
* The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect is close to the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Explanations
a. Downgraded two levels in imprecision: small numbers and broad CI.
b. Results not separated by number of doses of misoprostol received by women in the comparison arm.
c. Chai et al. *(1)* reported a median of 3.3 hours (range: 1.45–6.9) in the intervention group (buccal misoprostol) and 3.1 (range: 0.83–502) in the comparison group (sublingual misoprostol).
d. Downgraded one level: results only from one trial.

References
1. 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(4):480-5.

Comparison 4g: Routes of misoprostol administration in combination regimens (mifepristone plus misoprostol): 400 µg misoprostol administered orally compared with sublingually

Summary of Findings table for Comparison 4g

Outcome	Anticipated absolute effect* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comment
	Risk with 400 µg sublingual misoprostol	Risk with 400 µg oral misoprostol				
Efficacy: ongoing pregnancy	18 per 1000	**6 per 1000** (1–36)	**RR 0.44** (0.10–1.96)	564 (2 RCT) [1,2]	⊕⊕◯◯ LOW [a,b]	Our confidence in the direct estimate is limited; the true effect may be substantially different from the estimate of the effect
Efficacy: completed without surgical intervention	942 per 1000	**952 per 1000** (839–1000)	**RR 1.03** (0.99–1.07	564 (2 RCTs) [1,2]	⊕⊕◯◯ LOW [a,b]	Our confidence in the direct estimate is limited; the true effect may be substantially different from the estimate of the effect
Efficacy: expulsion time	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies)	—	No direct evidence identified
Safety: serious adverse events and complications, such as hospitalization, blood transfusion, need for further surgery beyond interventions to complete the removal of products, or death	0 per 1000	**0 per 1000** (0–0)	**RR 0.98** (0.01–49.14)	471 (1 RCT) [2]	⊕⊕◯◯ LOW [a–c]	Our confidence in the direct estimate is limited; the true effect may be substantially different from the estimate of the effect
Side-effects: bleeding	194 per 1000	**204 per 1000** (140–295)	**RR 1.05** (0.72–1.52)	470 (1 RCT) [2,d]	⊕⊕◯◯ LOW [a–c]	Our confidence in the direct estimate is limited; the true effect may be substantially different from the estimate of the effect
Side-effects: pain	339 per 1000	**336 per 1000** (261–428)	**RR 0.99** (0.77–1.26)	563 (2 RCTs) [1,2]	⊕◯◯◯ VERY LOW [c,e,f]	We are uncertain about the effect on this outcome because the certainty of the evidence is very low

Outcome	Anticipated absolute effect * (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comment
	Risk with 400 µg sublingual misoprostol	Risk with 400 µg oral misoprostol				
Side-effects: vomiting	410 per 1000	**447 per 1000** (328–554)	**RR 1.09** (0.80–1.35)	564 (2 RCTs) [1,2]	⊕◯◯◯ VERY LOW [e,f]	We are uncertain about the effect on this outcome because the certainty of the evidence is very low
Satisfaction	914 per 1000	**932 per 1000** (813–1000)	**RR 1.02** (0.89–1.18)	470 (1 RCT) [2]	⊕⊕◯◯ LOW [a,c]	Our confidence in the direct estimate is limited; the true effect may be substantially different from the estimate of the effect

CI: confidence interval; RCT: randomized controlled trial; RR: risk ratio

* The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect is close to the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Non-blinding of participants, providers and outcome assessors.
b. High risk for detection and performance bias.
c. Downgraded one level for inconsistency: only one trial included.
d. Defined in the study by Raghavan et al. *(2)* as more than the woman expected.
e. Downgraded one level: data self-reported and subject to recall bias.
f. Downgraded two levels for imprecision: few events and broad 95% CI.

References

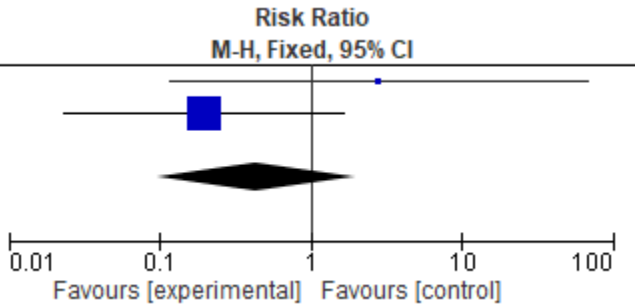
1. Dahiya K, Ahuja K, Dhingra A, Duhan N, Nanda S. Efficacy and safety of mifepristone and buccal misoprostol versus buccal misoprostol alone for medical abortion. Arch Gynecol Obstet. 2012;285(4):1055-8.
2. Raghavan S, Comendant R, Digol I, Ungureanu S, Friptu V, Bracken H, et al. Two-pill regimens of misoprostol after mifepristone medical abortion through 63 days' gestational age: a randomized controlled trial of sublingual and oral misoprostol. Contraception. 2009;79(2):84-90.

Forest plots for Comparison 4g

Analysis 1. Efficacy: ongoing pregnancy

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Dahaiya 2011	1	48	0	45	9.3%	2.82 [0.12, 67.40]
Raghavan 2009	1	238	5	233	90.7%	0.20 [0.02, 1.66]
Total (95% CI)		**286**		**278**	**100.0%**	**0.44 [0.10, 1.96]**
Total events	2		5			

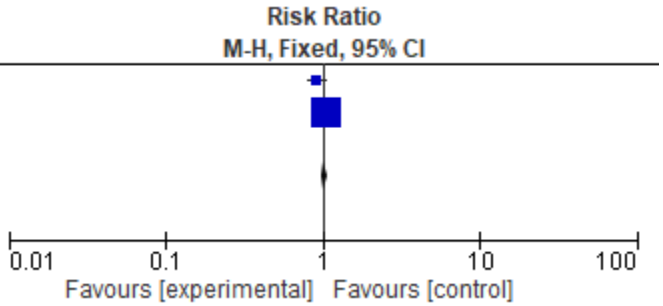
Heterogeneity: Chi² = 1.86, df = 1 (P = 0.17); I² = 46%
Test for overall effect: Z = 1.08 (P = 0.28)



Analysis 2. Efficacy: completed without surgical intervention

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Dahaiya 2011	42	48	43	45	16.7%	0.92 [0.81, 1.04]
Raghavan 2009	235	238	219	233	83.3%	1.05 [1.01, 1.09]
Total (95% CI)		**286**		**278**	**100.0%**	**1.03 [0.99, 1.07]**
Total events	277		262			

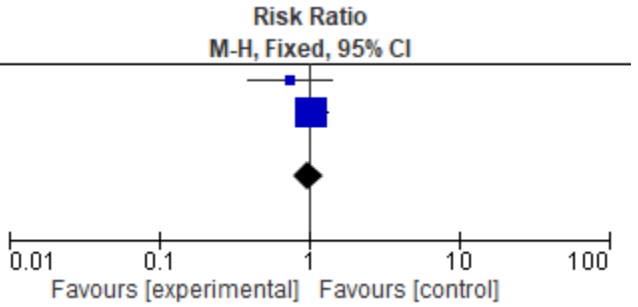
Heterogeneity: Chi² = 4.77, df = 1 (P = 0.03); I² = 79%
Test for overall effect: Z = 1.51 (P = 0.13)



Analysis 3. Side-effect: pain

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Dahaiya 2011	12	48	15	45	16.2%	0.75 [0.40, 1.42]
Raghavan 2009	84	238	79	233	83.8%	1.04 [0.81, 1.33]
Total (95% CI)		**286**		**278**	**100.0%**	**0.99 [0.79, 1.25]**
Total events	96		94			

Heterogeneity: Chi² = 0.87, df = 1 (P = 0.35); I² = 0%
Test for overall effect: Z = 0.05 (P = 0.96)

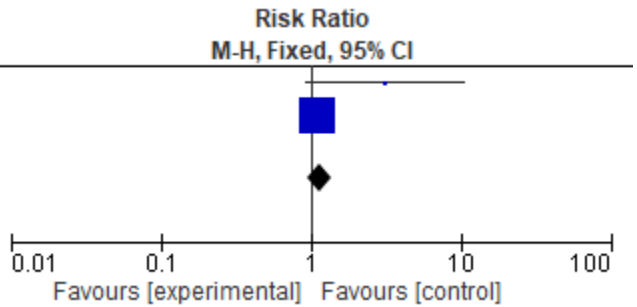


Analysis 4. Side-effect: vomiting

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Dahaiya 2011	10	48	3	45	2.7%	3.13 [0.92, 10.63]
Raghavan 2009	125	238	111	233	97.3%	1.10 [0.92, 1.32]
Total (95% CI)		**286**		**278**	**100.0%**	**1.16 [0.97, 1.39]**
Total events	135		114			

Heterogeneity: Chi² = 2.80, df = 1 (P = 0.09); I² = 64%

Test for overall effect: Z = 1.58 (P = 0.11)



Comparison 4h: Routes of misoprostol administration in combination regimens (mifepristone plus misoprostol): 800 µg misoprostol administered buccally compared with vaginally

Summary of Findings table for Comparison 4h

Outcome	Anticipated absolute effect* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comment
	Risk with 800 µg vaginal misoprostol	Risk with 800 µg buccal misoprostol				
Efficacy: ongoing pregnancy	19 per 1000	**9 per 1000** (2–50)	**RR 0.49** (0.09–2.68)	429 (1 RCT) [1,2]	⊕⊕◯◯ LOW [a,b]	Our confidence in the direct estimate is limited; the true effect may be substantially different from the estimate of the effect
Efficacy: completed without surgical intervention	934 per 1000	**934 per 1000** (813–1000)	**RR 1.00** (0.87–1.15)	429 (1 RCT) [1,2]	⊕⊕◯◯ LOW [a,b]	Our confidence in the direct estimate is limited; the true effect may be substantially different from the estimate of the effect
Efficacy: expulsion time	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies)	—	No direct evidence identified
Safety: serious adverse events and complications, such as hospitalization, blood transfusion, need for further surgery beyond interventions to complete the removal of products, or death	0 per 1000	**0 per 1000** (0–0)	**RR 2.94** (0.12–71.80)	429 (1 RCT) [1]	⊕⊕◯◯ LOW [a,b]	Our confidence in the direct estimate is limited; the true effect may be substantially different from the estimate of the effect
Side-effects: bleeding	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies)	—	No direct evidence identified
Side-effects: pain	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies)	—	No direct evidence identified

Outcome	Anticipated absolute effect* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comment
	Risk with 800 µg vaginal misoprostol	Risk with 800 µg buccal misoprostol				
Side-effects: vomiting	319 per 1000	**354 per 1000** (271–469)	**RR 1.11** (0.85–1.47)	429 (1 RCT) [1]	⊕⊕◯◯ LOW [a,b]	Our confidence in the direct estimate is limited; the true effect may be substantially different from the estimate of the effect
Satisfaction	948 per 1000	**929 per 1000** (805–1000)	**RR 0.98** (0.85–1.13)	423 (1 RCT) [1]	⊕⊕◯◯ LOW [a–c]	Our confidence in the direct estimate is limited; the true effect may be substantially different from the estimate of the effect

CI: confidence interval; RCT: randomized controlled trial; RR: risk ratio

* The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect is close to the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. High risk for performance and detection biases.
b. Downgraded one level for inconsistency: only one trial included.
c. Subject to recall bias.

References

1. Middleton T, Schaff E, Fielding SL, Scahill M, Shannon C, Westheimer E, et al. Randomized trial of mifepristone and buccal or vaginal misoprostol for abortion through 56 days of last menstrual period. Contraception. 2005;72(5):328-32.
2. Excluded (did not report on the critical outcome): Garg G, Takkar N, Sehgal A. Buccal versus vaginal misoprostol administration for the induction of first and second trimester abortions. J Obstet Gynaecol India. 2015;65(2):111-6.

Comparison 4i: Routes of misoprostol administration in combination regimens (mifepristone plus misoprostol): 400 µg misoprostol administered buccally compared with sublingually

Summary of Findings table for Comparison 4i

Outcome	Anticipated absolute effect* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comment
	Risk with 400 µg sublingual misoprostol	Risk with 400 µg buccal misoprostol				
Efficacy: ongoing pregnancy	15 per 1000	**23 per 1000** (3–165)	**RR 1.55** (0.22–11.03)	539 (1 RCT) [1]	⊕⊕◯◯ LOW [a,b]	Our confidence in the direct estimate is limited; the true effect may be substantially different from the estimate of the effect
Efficacy: completed without surgical intervention	974 per 1000	**954 per 1000** (886–1000)	**RR 0.98** (0.91–1.04)	539 (1 RCT) [1]	⊕⊕◯◯ LOW [a,b]	Our confidence in the direct estimate is limited; the true effect may be substantially different from the estimate of the effect
Efficacy: expulsion time	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies)	—	No direct evidence identified
Safety: serious adverse events and complications, such as hospitalization, blood transfusion, need for further surgery beyond interventions to complete the removal of products, or death	0 per 1000	**0 per 1000** (0–0)	**RR 0.33** (0.01–8.15)	539 (1 RCT) [1,c]	⊕⊕◯◯ LOW [a,b]	Our confidence in the direct estimate is limited; the true effect may be substantially different from the estimate of the effect
Side-effects: bleeding	562 per 1000	**1000 per 1000** (904–1000)	**RR 5.19** (1.61–6.79)	526 (1 RCT) [1]	⊕⊕◯◯ LOW [a,b]	Our confidence in the direct estimate is limited; the true effect may be substantially different from the estimate of the effect
Side-effects: pain	800 per 1000	**752 per 1000** (672–856)	**RR 0.94** (0.84–1.07)	526 (1 RCT) [1]	⊕⊕◯◯ LOW [a,b]	Our confidence in the direct estimate is limited; the true effect may be substantially different from the estimate of the effect

Outcome	Anticipated absolute effect * (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comment
	Risk with 400 µg sublingual misoprostol	Risk with 400 µg buccal misoprostol				
Side-effects: vomiting	219 per 1000	**335 per 1000** (235–482)	**RR 1.53** (1.07–2.20)	526 (1 RCT) [1]	⊕⊕◯◯ LOW [a,b]	Our confidence in the direct estimate is limited; the true effect may be substantially different from the estimate of the effect
Satisfaction	958 per 1000	**978 per 1000** (872–1000)	**RR 1.02** (0.91–1.16)	533 (1 RCT) [1]	⊕⊕◯◯ LOW [b,d]	Our confidence in the direct estimate is limited; the true effect may be substantially different from the estimate of the effect

CI: confidence interval; RCT: randomized controlled trial; RR: risk ratio

* The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect is close to the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Both studies unblinded (providers, participants and outcome assessors). Risk of selection bias, with unclear allocation concealment.
b. Downgraded one level for inconsistency: only one trial included.
c. Maternal death due to *C. sordellii* infection.
d. Subject to recall and courtesy biases.

References

1. 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(6):513-9.

Comparison 4j: Routes of misoprostol administration in combination regimens (mifepristone plus misoprostol): 800 µg misoprostol administered orally compared with buccally

Summary of Findings table for Comparison 4j

Outcome	Anticipated absolute effect * (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comment
	Risk with 800 µg buccal misoprostol	Risk with 800 µg oral misoprostol				
Efficacy: ongoing pregnancy	10 per 1000	**34 per 1000** (11–103)	**RR 3.61** (1.20–10.80)	847 (1 RCT) [1]	⊕⊕◯◯ LOW [a,b]	Our confidence in the direct estimate is limited; the true effect may be substantially different from the estimate of the effect
Efficacy: completed without surgical intervention	962 per 1000	**933 per 1000** (847–1000)	**RR 0.97** (0.88–1.07)	847 (1 RCT) [1]	⊕⊕◯◯ LOW [c,d]	Our confidence in the direct estimate is limited; the true effect may be substantially different from the estimate of the effect
Efficacy: expulsion time	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies)	—	No direct evidence identified
Safety: serious adverse events and complications, such as hospitalization, blood transfusion, need for further surgery beyond interventions to complete the removal of products, or death	2 per 1000	**1 per 1000** (0–19)	**RR 0.33** (0.01–8.08)	847 (1 RCT) [1,e]	⊕⊕◯◯ LOW [c,d]	Our confidence in the direct estimate is limited; the true effect may be substantially different from the estimate of the effect
Side-effects: bleeding	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies)	—	No direct evidence identified
Side-effects: pain	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies)	—	No direct evidence identified
Side-effects: vomiting	476 per 1000	**447 per 1000** (376–528)	**RR 0.94** (0.79–1.11)	830 (1 RCT) [1]	⊕⊕◯◯ LOW [d]	Our confidence in the direct estimate is limited; the true effect may be substantially different from the estimate of the effect

Outcome	Anticipated absolute effect * (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comment
	Risk with 800 µg buccal misoprostol	Risk with 800 µg oral misoprostol				
Satisfaction	911 per 1000	**929 per 1000** (829–1000)	**RR 1.02** (0.91–1.12)	835 (1 RCT) [1]	⨁⨁◯◯ LOW [d]	Our confidence in the direct estimate is limited; the true effect may be substantially different from the estimate of the effect

CI: confidence interval; RCT: randomized controlled trial; RR: risk ratio

* The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect is close to the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Downgraded for high risk of reporting and detection biases. Reporting bias: outcome of time to expulsion not reported although it was stated as an outcome. High risk for selection bias, with unclear randomization and allocation.
b. Misoprostol administered at 24 or 48 hours in the comparison arm.
c. Study participants and providers not blinded. Unclear if outcome assessment was blinded.
d. Downgraded one level: results from only one trial.
e. There was one surgery for ruptured ectopic pregnancy in the study by Chai et al *(1)*.

References

1. 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(4):480-5.

Comparison 4k: Routes of misoprostol administration in combination regimens (mifepristone plus misoprostol): excluded studies

Two studies were identified but excluded as they did not report on the primary outcome. Arvidsson et al. *(1)* compared 400 µg misoprostol given orally with 800 µg misoprostol given vaginally. Aubeny and Chatellier *(2)* compared a dose of 400 µg misoprostol given orally versus vaginally.

References

1. Arvidsson C, Hellborg M, Gemzell-Danielsson K. Preference and acceptability of oral versus vaginal administration of misoprostol in medical abortion with mifepristone. Eur J Obstet Gynecol Reprod Biol. 2005;123(1):87-91.
2. Aubeny E, Chatellier G. A randomized comparison of mifepristone and self-administered oral or vaginal misoprostol for early abortion. Eur J Contracept Reprod Health Care. 2000;5(3):171-6.

Comparison 5: Medical management (800 µg vaginal misoprostol) compared with surgical management

Summary of Findings table for Comparison 5

Outcome	Anticipated absolute effect* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comment
	Risk with surgical management	Risk with 800 µg vaginal misoprostol				
Efficacy: ongoing pregnancy	0 per 1000	**0 per 1000** (0–0)	**RR 6.70** (1.88–23.86)	137 (1 RCT) [1]	⊕◯◯◯ VERY LOW [a–d]	We are uncertain about the effect on this outcome because the certainty of the evidence is very low
Efficacy: completed without surgical intervention	956 per 1000	**975 per 1000** (851–1000)	**RR 1.02** (0.89–1.17)	137 (1 RCT) [1]	⊕◯◯◯ VERY LOW [a–d]	We are uncertain about the effect on this outcome because the certainty of the evidence is very low
Efficacy: expulsion time < 24 h	956 per 1000	**679 per 1000** (497–927)	**RR 0.71** (0.52–0.97)	137 (1 RCT) [1]	⊕◯◯◯ VERY LOW [a–d]	We are uncertain about the effect on this outcome because the certainty of the evidence is very low
Safety: serious adverse events and complications, such as hospitalization, blood transfusion, need for further surgery beyond interventions to complete the removal of products, or death	15 per 1000	**5 per 1000** (0–118)	**RR 0.33** (0.01–8.04)	137 (1 RCT) [1]	⊕◯◯◯ VERY LOW [a–d]	We are uncertain about the effect on this outcome because the certainty of the evidence is very low
Side-effects: bleeding	0 per 1000	**0 per 1000** (0–0)	**RR 6.60** (0.34–125.00)	137 (1 RCT) [1,e]	⊕◯◯◯ VERY LOW [a–d]	We are uncertain about the effect on this outcome because the certainty of the evidence is very low
Side-effects: pain	1000 per 1000	**700 per 1000** (510–950)	**RR 0.70** (0.51–0.95)	137 (1 RCT) [1,f]	⊕◯◯◯ VERY LOW [a–d]	We are uncertain about the effect on this outcome because the certainty of the evidence is very low

Outcome	Anticipated absolute effect * (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comment
	Risk with surgical management	Risk with 800 µg vaginal misoprostol				
Side-effects: vomiting	29 per 1000	**56 per 1000** (11–297)	**RR 1.91** (0.36–10.10)	137 (1 RCT) [1]	⊕◯◯◯ VERY LOW [a–d]	We are uncertain about the effect on this outcome because the certainty of the evidence is very low
Satisfaction	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies) [g]	—	No direct evidence identified

CI: confidence interval; RCT: randomized controlled trial; RR: risk ratio

* The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect is close to the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Non-blinding of participants, providers and outcome assessors. Inadequate randomization strategy : relied on the use of even/odd numbers.
b. Downgraded one level for inconsistency : only one trial included.
c. Study included women with estimated gestational age to 49 days only.
d. Downgraded two levels for imprecision: few events and broad 95% CI.
e. Defined by Prasad et al. *(1)* as more than their regular menstruation, evaluated by patient self-assessment using a pictorial chart.
f. Patients were asked to self-report if pain was mild, moderate or severe. It is unclear from the manuscript by Prasad et al. *(1)* if the numbers (of women reporting pain) reflect any pain, or one of these subcategories.
g. Results not reported by group. Prasad et al. *(1)* noted that, overall, "132/137 opted for medical method of abortion irrespective of previous experience with abortion".

References

1. Prasad S, Kumar A, Divya A. Early termination of pregnancy by single-dose 800 microg misoprostol compared with surgical evacuation. Fertil Steril. 2009;91(1):28-31.

Comparison 6a: Dose and interval in misoprostol-only regimens: 400 µg orally every 3 hours (4 doses) compared with 600 µg vaginally once

Summary of Findings table for Comparison 6a

Outcome	Anticipated absolute effect * (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comment
	Risk with 600 µg vaginal misoprostol once	Risk with 400 µg oral misoprostol every 3 h (for 4 doses)				
Efficacy: ongoing pregnancy	200 per 1000	**300 per 1000** (134–660)	**RR 1.50** (0.67–3.30)	76 (1 RCT) [1]	⊕◯◯◯ VERY LOW [a–d]	We are uncertain about the effect on this outcome because the certainty of the evidence is very low
Efficacy: completed without surgical intervention	425 per 1000	**399 per 1000** (221–722)	**RR 0.94** (0.52–1.70)	76 (1 RCT) [1]	⊕◯◯◯ VERY LOW [a–d]	We are uncertain about the effect on this outcome because the certainty of the evidence is very low
Efficacy: expulsion time < 24 h	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies)	—	No direct evidence identified
Safety: serious adverse events and complications, such as hospitalization, blood transfusion, need for further surgery beyond interventions to complete the removal of products, or death	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies)	—	No direct evidence identified
Side-effects: bleeding	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies) [e]	—	No direct evidence identified
Side-effects: pain	950 per 1000	**941 per 1000** (684–1000)	**RR 0.99** (0.72–1.40)	76 (1 RCT) [1]	⊕◯◯◯ VERY LOW [a–d]	We are uncertain about the effect on this outcome because the certainty of the evidence is very low
Side-effects: vomiting	75 per 1000	**285 per 1000** (87–930)	**RR 3.80** (1.16–12.40)	76 (1 RCT) [1]	⊕◯◯◯ VERY LOW [a–d]	We are uncertain about the effect on this outcome because the certainty of the evidence is very low

Outcome	Anticipated absolute effect * (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comment
	Risk with 600 µg vaginal misoprostol once	Risk with 400 µg oral misoprostol every 3 h (for 4 doses)				
Satisfaction	450 per 1000	**405 per 1000** (225–720)	**RR 0.9** (0.5–1.6)	76 (1 RCT) [1]	⨁◯◯◯ VERY LOW [b–d]	We are uncertain about the effect on this outcome because the certainty of the evidence is very low

CI: confidence interval; RCT: randomized controlled trial; RR: risk ratio
* The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect is close to the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Explanations
a. High risk for performance and detection bias.
b. Downgraded one level for inconsistency: only one trial included.
c. Study included women with estimated gestational age to 56 days only.
d. Downgraded two levels for imprecision: few events and broad 95% CI.
e. Blanchard et al. *(1)* reported 1.2 mean days of heavy bleeding in the intervention group (400 µg oral misoprostol every 3 hours, for 4 doses) versus 2.2 days in the comparison group (600 µg vaginal misoprostol once).

References
1. Blanchard K, Shochet T, Coyaji K, Ngoc Nguyen TN, Winikoff B. Misoprostol alone for early abortion: an evaluation of seven potential regimens. Contraception. 2005;72(2):91-7.

Comparison 6b: Dose and interval in misoprostol-only regimens: 800 µg orally every 6 hours (2 doses) compared with 600 µg vaginally once

Summary of Findings table for Comparison 6b

Outcome	Anticipated absolute effect * (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comment
	Risk with 600 µg vaginal misoprostol once	Risk with 800 µg oral misoprostol every 6 h (for 2 doses)				
Efficacy: ongoing pregnancy	200 per 1000	**172 per 1000** (56–518)	**RR 0.86** (0.28–2.59)	64 (1 RCT) [1]	⊕◯◯◯ VERY LOW [a–d]	We are uncertain about the effect on this outcome because the certainty of the evidence is very low
Efficacy: completed without surgical intervention	425 per 1000	**476 per 1000** (259–871)	**RR 1.12** (0.61–2.05)	64 (1 RCT) [1]	⊕◯◯◯ VERY LOW [a–d]	We are uncertain about the effect on this outcome because the certainty of the evidence is very low
Efficacy: expulsion time < 24 h	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies)	—	No direct evidence identified
Safety: serious adverse events and complications, such as hospitalization, blood transfusion, need for further surgery beyond interventions to complete the removal of products, or death	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies)	—	No direct evidence identified
Side-effects: bleeding	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies) [e]	—	No direct evidence identified
Side-effects: pain	950 per 1000	**950 per 1000** (656–1000)	**RR 1.00** (0.69–1.45)	64 (1 RCT) [1]	⊕◯◯◯ VERY LOW [a–d]	We are uncertain about the effect on this outcome because the certainty of the evidence is very low
Side-effects: vomiting	75 per 1000	**215 per 1000** (58–788)	**RR 2.87** (0.77–10.50)	64 (1 RCT) [1]	⊕◯◯◯ VERY LOW [a–d]	We are uncertain about the effect on this outcome because the certainty of the evidence is very low

Outcome	Anticipated absolute effect * (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comment
	Risk with 600 µg vaginal misoprostol once	Risk with 800 µg oral misoprostol every 6 h (for 2 doses)				
Satisfaction	450 per 1000	**455 per 1000** (243–846)	**RR 1.01** (0.54–1.88)	64 (1 RCT) [1]	⨁◯◯◯ VERY LOW [b–d]	No direct evidence identified

CI: confidence interval; RCT: randomized controlled trial; RR: risk ratio
* The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect is close to the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Explanations
a. High risk for performance and detection biases.
b. Downgraded one level for inconsistency: only one trial included.
c. Study included women with estimated gestational age to 56 days only.
d. Downgraded two levels for imprecision: few events and broad 95% CI.
e. Blanchard et al. *(1)* reported 1.2 mean days of heavy bleeding for the intervention group (800 µg oral misoprostol every 6 hours, for 2 doses) versus 2.2 days for the comparison group (600 µg vaginal misoprostol once).

References
1. Blanchard K, Shochet T, Coyaji K, Ngoc Nguyen TN, Winikoff B. Misoprostol alone for early abortion: an evaluation of seven potential regimens. Contraception. 2005;72(2):91-7.

Comparison 6c: Dose and interval in misoprostol-only regimens: 400 µg orally every 3 hours (4 doses) compared with 800 µg orally every 6 hours (2 doses)

Summary of Findings table for Comparison 6c

Outcome	Anticipated absolute effect * (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comment
	Risk with 800 µg oral misoprostol every 6 h (for 2 doses)	Risk with 400 µg oral misoprostol every 3 h (for 4 doses)				
Efficacy: ongoing pregnancy	167 per 1000	**292 per 1000** (103–817)	**RR 1.75** (0.62–4.90)	60 (1 RCT) [1]	⊕◯◯◯ VERY LOW [a–d]	We are uncertain about the effect on this outcome because the certainty of the evidence is very low
Efficacy: completed without surgical intervention	500 per 1000	**420 per 1000** (220–795)	**RR 0.84** (0.44–1.59)	60 (1 RCT) [1]	⊕◯◯◯ VERY LOW [a–d]	We are uncertain about the effect on this outcome because the certainty of the evidence is very low
Efficacy: expulsion time < 24 h	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies)	—	No direct evidence identified
Safety: serious adverse events and complications, such as hospitalization, blood transfusion, need for further surgery beyond interventions to complete the removal of products, or death	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies)	—	No direct evidence identified
Side-effects: bleeding	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies) [e]	—	No direct evidence identified
Side-effects: pain	958 per 1000	**958 per 1000** (661–1000)	**RR 1.00** (0.69–1.45)	60 (1 RCT) [1]	⊕◯◯◯ VERY LOW [a–d]	We are uncertain about the effect on this outcome because the certainty of the evidence is very low

Outcome	Anticipated absolute effect * (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comment
	Risk with 800 µg oral misoprostol every 6 h (for 2 doses)	Risk with 400 µg oral misoprostol every 3 h (for 4 doses)				
Side-effects: vomiting	250 per 1000	**333 per 1000** (140–780)	**RR 1.33** (0.56–3.12)	60 (1 RCT) [1]	⊕◯◯◯ VERY LOW [a–d]	We are uncertain about the effect on this outcome because the certainty of the evidence is very low
Satisfaction	458 per 1000	**408 per 1000** (211–788)	**RR 0.89** (0.46–1.72)	60 (1 RCT) [1]	⊕◯◯◯ VERY LOW [b–d]	We are uncertain about the effect on this outcome because the certainty of the evidence is very low

CI: confidence interval; RCT: randomized controlled trial; RR: risk ratio
* The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect is close to the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. High risk for performance and detection bias.
b. Downgraded one level for inconsistency: only one trial included.
c. Study included women with estimated gestational age to 56 days only.
d. Downgraded two levels for imprecision: few events and broad 95% CI.
e. Blanchard et al. *(1)* reported 1.2 mean days of heavy bleeding for the intervention group (800 µg oral misoprostol every 6 hours, for 2 doses) versus 2.1 days for the comparison group (400 µg oral misoprostol every 3 hours, for 4 doses).

References

1. Blanchard K, Shochet T, Coyaji K, Ngoc Nguyen TN, Winikoff B. Misoprostol alone for early abortion: an evaluation of seven potential regimens. Contraception. 2005;72(2):91-7.

II. Determine appropriate regimens for early medical abortion provision at > 63 days and up to 84 days of gestation

Comparison 1: Combination regimens (mifepristone plus misoprostol) compared with misoprostol-only regimens

One study was identified that compared mifepristone plus misoprostol with misoprostol alone for medical abortions at > 63 days and up to 84 days gestational age. For the critical outcome, ongoing pregnancy, there was a serious discrepancy in the numbers reported. In Table 2 of the paper by Dalenda et al. *(1)*, 7/73 women in the combined group versus 4/49 in the misoprostol-only group are reported as having curettage for persistent gestational sac ($P = 0.56$). In the text below the table, the authors report that 7/73 women in the combined group versus 9/49 women in the misoprostol-only group had curettage for continuing pregnancy. We attempted to contact the authors by email, phone and social media multiple times to clarify these numbers but received no answer. The study was thus excluded as we could not reliably determine the critical outcome.

Reference

1. 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.

Comparison 2: Doses of misoprostol in combination regimens (mifepristone plus misoprostol)

No studies were identified that compared different doses of misoprostol in combined regimens while maintaining the same route of administration. One study was identified that compared different doses of misoprostol but the route was also varied. This paper is discussed in the following GRADE profile, for Comparison 3.

Reference

1. Hamoda H, Ashok PW, Flett GM, Templeton A. A randomised controlled trial of mifepristone in combination with misoprostol administered sublingually or vaginally for medical abortion up to 13 weeks of gestation. BJOG. 2005;112(8):1102-8.

Comparison 3: Doses and routes of misoprostol in combination regimens (mifepristone plus misoprostol): 800 µg vaginal compared with 600 µg sublingual

Summary of Findings table for Comparison 3

Outcome	Anticipated absolute effect* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comment
	Risk with 600 µg sublingual misoprostol	Risk with 800 µg vaginal misoprostol				
Efficacy: ongoing pregnancy	19 per 1000	**0 per 1000** (0–0)	Not estimable	192 (1 RCT) [1]	⊕◯◯◯ VERY LOW [a–c]	Our confidence in the direct estimate is limited; the true effect may be substantially different from the estimate of the effect
Efficacy: completed without surgical intervention	971 per 1000	**969 per 1000** (932–986)	**OR 0.91** (0.40–2.04)	192 (1 RCT) [1]	⊕◯◯◯ VERY LOW [a–c]	Our confidence in the direct estimate is limited; the true effect may be substantially different from the estimate of the effect
Efficacy: expulsion time	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies)	—	No direct evidence identified
Safety: serious adverse events and complications, such as hospitalization, blood transfusion, need for further surgery beyond interventions to complete the removal of products, or death	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies)	—	No direct evidence identified
Side-effects: bleeding, pain and vomiting	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies)	—	No direct evidence identified
Satisfaction	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies)	—	No direct evidence identified

CI: confidence interval; OR: odds ratio; RCT: randomized controlled trial

* The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect is close to the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Downgraded one level for inconsistency: only one trial included.
b. Indirectness of evidence: population includes women up to 91 days gestational age.
c. Downgraded two levels for imprecision: population includes women up to 91 days gestational age, few events and broad 95% CI.

References

1. Hamoda H, Ashok PW, Flett GM, Templeton A. A randomised controlled trial of mifepristone in combination with misoprostol administered sublingually or v aginally for medical abortion up to 13 weeks of gestation. BJOG. 2005;112(8):1102-8.

Comparison 4a: Doses in misoprostol-only regimens: 200 µg compared with 400 µg vaginal misoprostol

Summary of Findings for Comparison 4

Outcomes	Anticipated absolute effects * (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with 400 µg vaginal misoprostol	Risk with 200 µg vaginal misoprostol				
Efficacy: ongoing pregnancy	0 per 1000	**0 per 1000** (0–0)	**RR 7.00** (0.37–132.10)	100 (1 RCT) [1]	⊕◯◯◯ VERY LOW [a–c]	Our confidence in the direct estimate is limited; the true effect may be substantially different from the estimate of the effect Khazardoost et al. *(1)* reported ongoing pregnancy as "treatment failure"
Efficacy: completed without surgical intervention	542 per 1000	**493 per 1000** (390–612)	**RR 0.91** (0.72–1.13)	203 (2 RCTs) [1,2,d]	⊕⊕◯◯ LOW [b,e]	Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect Khazardoost et al. *(1)* did not define complete abortion and did not report what they did with those who needed additional intervention
Efficacy: expulsion time from initiation of treatment	459 per 1000	**363 per 1000** (239–551)	**RR 0.79** (0.52–1.20)	334 (2 RCTs) [1,2,d]	⊕⊕◯◯ LOW [b,e]	Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect
Safety: serious adverse events and complications, such as hospitalization, blood transfusion, need for further surgery beyond interventions to complete the removal of products, or death	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies)	—	No direct evidence identified Serious adverse events outcomes not reported by different doses
Side-effects: nausea	40 per 1000	**8 per 1000** (4–162)	**RR 0.20** (0.10–4.06)	100 (1 RCT) [1]	⊕◯◯◯ VERY LOW [a,b,f]	Our confidence in the direct estimate is limited; the true effect may be substantially different from the estimate of the effect
Side-effects: vomiting	40 per 1000	**40 per 1000** (6–273)	**RR 1.00** (0.15–6.82)	100 (1 RCT) [1]	⊕◯◯◯ VERY LOW [a,b]	Our confidence in the direct estimate is limited; the true effect may be substantially different from the estimate of the effect
Side-effects: fever	280 per 1000	**101 per 1000** (39–258)	**RR 0.36** (0.14–0.92)	100 (1 RCT) [1]	⊕◯◯◯ VERY LOW [a,b]	Our confidence in the direct estimate is limited; the true effect may be substantially different from the estimate of the effect
Side-effects: diarrhoea	20 per 1000	**7 per 1000** (0–160)	**RR 0.33** (0.01–7.99)	100 (1 RCT) [1]	⊕◯◯◯ VERY LOW [a,b]	Our confidence in the direct estimate is limited; the true effect may be substantially different from the estimate of the effect

Side-effects: severe pelvic pain	280 per 1000	**81 per 1000** (28–227)	**RR 0.29** (0.10–0.81)	100 (1 RCT) [1]	⊕◯◯◯ VERY LOW [a,b]	Our confidence in the direct estimate is limited; the true effect may be substantially different from the estimate of the effect
Satisfaction	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies)	—	No direct evidence identified. Satisfaction/acceptability outcomes not reported by different doses.

CI: confidence interval; RCT: randomized controlled trial; RR: risk ratio

* The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect is close to the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Khazardoost et al. *(1)* downgraded to "serious", with high risk of bias for performance and detection biases, and unclear risk of bias for selection and other biases.
b. Downgraded two levels for indirect evidence: around half of the patients from the study had early pregnancy failures.
c. Downgraded one level for imprecision: few events and wide CI.
d. One RCT and one prospective cohort study.
e. Downgraded one level: Bugalho et al. *(2)* had a high risk of bias for selection bias and reporting bias; Khazardoost *(1)* had a high risk of bias for performance bias and detection bias.
f. Downgraded one level: few events.

References

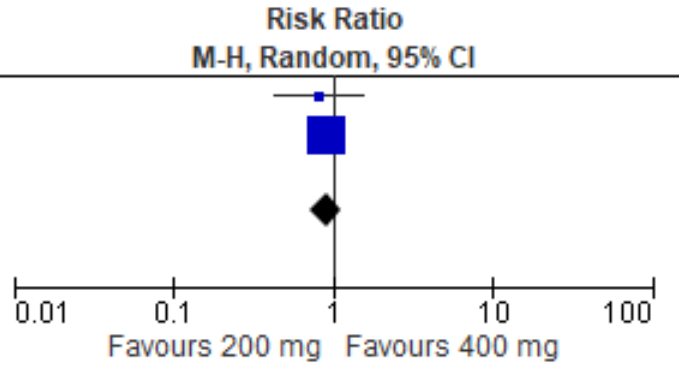
1. Khazardoost S, Hantoushzadeh S, Madani MM. A randomised trial of two regimens of vaginal misoprostol to manage termination of pregnancy of up to 16 weeks. Aust N Z J Obstet Gynaecol. 2007;47(3):226-9.
2. Bugalho A, Faúndes A, Jamisse L, Usfá M, Maria E, Bique C. Evaluation of the effectiveness of vaginal misoprostol to induce first trimester abortion. Contraception. 1996;53(4):244-6.

Forest plots for Comparison 4a

Analysis 1. Efficacy: completed without additional surgical intervention

Study or Subgroup	200 mg Events	200 mg Total	400 mg Events	400 mg Total	Weight	Risk Ratio M-H, Random, 95% CI
Bugalho 1996	14	57	14	46	12.6%	0.81 [0.43, 1.52]
Khazardoost 2007	35	50	38	50	87.4%	0.92 [0.73, 1.17]
Total (95% CI)		**107**		**96**	**100.0%**	**0.91 [0.72, 1.13]**
Total events	49		52			

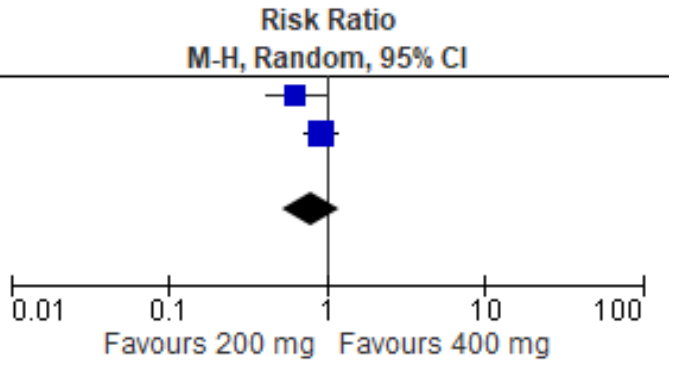
Heterogeneity: Tau² = 0.00; Chi² = 0.18, df = 1 (P = 0.67); I² = 0%
Test for overall effect: Z = 0.87 (P = 0.39)



Analysis 2. Efficacy: expulsion time

Study or Subgroup	200 mg Events	200 mg Total	400 mg Events	400 mg Total	Weight	Risk Ratio M-H, Random, 95% CI
Bugalho 1996	22	101	46	133	40.8%	0.63 [0.41, 0.98]
Khazardoost 2007	35	50	38	50	59.2%	0.92 [0.73, 1.17]
Total (95% CI)		**151**		**183**	**100.0%**	**0.79 [0.52, 1.20]**
Total events	57		84			

Heterogeneity: Tau² = 0.06; Chi² = 2.92, df = 1 (P = 0.09); I² = 66%
Test for overall effect: Z = 1.11 (P = 0.27)



Comparison 4b: Doses in misoprostol-only regimens: single-dose versus multiple-dose misoprostol: excluded study

van Bogaert and Misra *(1)* also compared different regimens of misoprostol only for late first-trimester abortion. This study compared 400 µg of sublingual misoprostol followed by vaginally or orally administered 800 µg misoprostol every 8 hours. Complete abortion rates were higher among the vaginal group than among the oral group (93.4% compared with 86.9%) and the only factor associated with need for repeat misoprostol doses in a linear regression analysis was increasing gestational age. This study was excluded from the GRADE table as it reported the whole first trimester as gestational age, so we were unable to use the data to answer questions specific to our gestational age of interest.

References

1. van Bogaert LJ, Misra A. Anthropometric characteristics and success rates of oral or vaginal misoprostol for pregnancy termination in the first and second trimesters. Int J Gynaecol Obstet. 2010;109(3):213-5.

Comparison 5: Combination regimen of mifepristone (200 mg oral) plus misoprostol (800 µg vaginal) compared with vacuum aspiration

Summary of Findings table for Comparison 5

Outcome	Anticipated absolute effect* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comment
	Risk with vacuum aspiration	Risk with 200 mg oral mifepristone and 800 µg vaginal misoprostol				
Efficacy: ongoing pregnancy	0 per 1000	**0 per 1000** (0–0)	**OR 0.12** (0.01–2.30)	445 (1 RCT) [1]	⊕⊕◯◯ LOW [a–c]	There may be little or no difference in the number of women with ongoing pregnancies who had medical or surgical abortions
Efficacy: completed without surgical intervention	983 per 1000	**984 per 1000** (979–988)	**OR 1.03** (0.80–1.36)	445 (1 RCT) [1]	⊕⊕◯◯ LOW [a,c]	There may be little or no difference in the number of women with surgical intervention to complete termination of pregnancy
Efficacy: expulsion time from initiation of treatment	0 per 1000	**0 per 1000** (0–0)	Not estimable	(0 studies)	—	No direct evidence identified
Safety: serious adverse events (transfusion)	4 per 1000	**10 per 1000** (0–205)	**OR 2.52** (0.10–62.10)	445 (1 RCT) [1]	⊕⊕◯◯ LOW [a,c]	There may be little or no difference in the number of women with transfusions who had medical or surgical abortions
Side-effects: nausea	278 per 1000	**133 per 1000** (94–185)	**OR 0.40** (0.27–0.59)	366 (1 RCT) [1]	⊕⊕◯◯ LOW [a,c]	There may be little or no difference in the number of women with nausea who had medical or surgical abortions
Side-effects: vomiting	83 per 1000	**15 per 1000** (8–27)	**OR 0.17** (0.09–0.30)	366 (1 RCT) [1]	⊕⊕◯◯ LOW [a,c]	There may be little or no difference in the number of women with vomiting who had medical or surgical abortions
Side-effects: diarrhoea	44 per 1000	**5 per 1000** (2–10)	**OR 0.10** (0.05–0.22)	366 (1 RCT) [1]	⊕⊕⊕◯ MODERATE [a,c]	There is probably little or no difference in the number of women with diarrhoea among those receiving medical versus surgical abortion
Satisfaction	792 per 1000	**811 per 1000** (727–874)	**OR 1.13** (0.70–1.82)	163 (1 RCT) [1]	⊕◯◯◯ VERY LOW [a,c,d]	We are uncertain about the effect on this outcome because the certainty of the evidence is very low

CI: confidence interval; OR: odds ratio; RCT: randomized controlled trial

* The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect is close to the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Downgraded two levels because of risk of bias, including partial randomization, unblinded study and unclear randomization across outcomes reported.
b. Partially randomized patient preference trial. Those who chose their treatment appeared similar on demographic data and gestational age. Risk of bias high due to partial randomization and not all outcomes being reported by whether they were randomized or not, due to unclear blinding of outcome assessment and due to being a non-blinded study.
c. Downgraded two levels due to imprecision: small numbers and broad CI.
d. Downgraded for risk of bias: only 35% of women in the medical abortion group and 53.3% in surgical abortion group answered the question on preferred future method of abortion.

Reference

1. Ashok PW, Kidd A, Flett GM, Fitzmaurice A, Graham W, Templeton A. A randomized comparison of medical abortion and surgical vacuum aspiration at 10–13 weeks gestation. Hum Reprod. 2002;17(1):92-8.

Comparison 6a: Management of induced abortion in a health-care facility compared with self-management/home care

Summary of Findings table for Comparison 6a

Outcome	Anticipated absolute effect* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comment
	Risk with home care	Risk with health-care facility				
Efficacy: ongoing pregnancy	—	—	—	—	—	No direct evidence identified Efficacy outcomes not reported by location
Efficacy: completed without surgical intervention	—	—	—	—	—	No direct evidence identified Efficacy outcomes not reported by location
Efficacy: expulsion time from initiation of treatment	—	—	—	—	—	No direct evidence identified Efficacy outcomes not reported by location
Safety: serious adverse events and complications, such as hospitalization, blood transfusion, need for further surgery beyond interventions to complete the removal of products, or death	—	—	—	—	—	No direct evidence identified Safety outcomes not reported by location
Side-effects: bleeding	—	—	—	—	—	No direct evidence identified Side-effect outcomes not reported by location
Side-effects: pain	—	—	—	—	—	No direct evidence identified Side-effect outcomes not reported by location
Side-effects: vomiting	—	—	—	—	—	No direct evidence identified Side-effect outcomes not reported by location
Satisfaction	98 per 100	**100 per 100** (20–100)	**RR 1.00** (0.98–1.03)	285 (1 observational study) [1]	⊕◯◯◯ VERY LOW [a–c]	Our confidence in the direct estimate is limited; the true effect may be substantially different from the estimate of the effect Women chose their treatment group, which may impact satisfaction

CI: confidence interval; RR: risk ratio

* The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect is close to the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Downgraded two levels for high risk of bias (selection bias, performance bias, detection bias and reporting bias) in five of the seven domains.
b. Downgraded one level for indirectness: only one small study identified.
c. Downgraded one level for imprecision: few events and wide 95% CI.

Reference

1. Plataisa I, Tsereteli T, Grebennikova G, Lotarevich T, Winikoff B. Prospective study of home use of mifepristone and misoprostol for medical abortion up to 10 weeks of pregnancy in Kazakhstan. Int J Gynaecol Obstet. 2016. 134(3):268-71.

Comparison 6b: Management of induced abortion in a health-care facility compared with self-management/home care: excluded studies

Two additional studies investigated outpatient medical abortion up to 70 days gestation; the comparison, however, was of an earlier gestational week (57–63 days) versus the next gestational week (64–70 days). Both studies were therefore excluded from the GRADE table.

Bracken et al. *(1)* compared the effectiveness and acceptability of outpatient medical abortion (200 mg mifepristone followed 24–48 hours later by 400 µg sublingual misoprostol) at 64–70 days versus medical abortion at 57–63 days gestational age. A total of 714 women were enrolled across four countries (Georgia, India, Tunisia and Ukraine). No significant difference in abortion efficacy was noted between the earlier and later gestational age groups, with 94.8% and 91.9% (risk ratio 0.79, confidence interval 0.61–1.04) reporting complete abortions, respectively. The rate of surgical intervention for excessive or prolonged bleeding was significantly greater for the later gestational age (2.5% versus 0.5% for the earlier gestational age). No significant difference was noted between groups in terms of serious adverse events, such as the need for blood transfusion (one in each group) or hospital admission (one in the earlier and two in the later gestational age group).

Winikoff et al. *(2)* investigated the effectiveness and acceptability of outpatient medical abortion (200 mg mifepristone followed 24–48 hours later by 800 µg buccal misoprostol) at gestational ages 57–63 days compared with 64–70 days in their trial in the United States of America enrolling 729 women. They also reported side-effects (chills, fever, vomiting, nausea, diarrhoea and heavy bleeding) with no significant differences between the two groups except for more vomiting in the later than in the earlier gestational age group (45.7% versus 35.8%, $P = 0.008$).

References

1. Bracken H, Dabash R, Tsertsvadze G, Posohova S, Shah M, Hajri S, et al. A two-pill sublingual misoprostol outpatient regimen following mifepristone for medical abortion through 70 days' LMP: a prospective comparative open-label trial. Contraception. 2014;89(3):181-6.
2. 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(5):1070-6.