Evidence tables for review question: Is the combination of mifepristone and misoprostol more effective than misoprostol alone in the medical management of missed miscarriage?

Chu, 2020

Bibliographic Reference	Chu JJ; Devall AJ; Beeson LE; Hardy P; Cheed V; Sun Y; Roberts TE; Ogwulu CO; Williams E; Jones LL; La Fontaine Papadopoulos JH; Bender-Atik R; Brewin J; Hinshaw K; Choudhary M; Ahmed A; Naftalin J; Nunes N; Oliver A; Izzat F; Bhatia K; Hassan I; Jeve Y; Hamilton J; Deb S; Bottomley C; Ross J; Watkins L; Underwood M; Cheong Y; Kumar CS; Gupta P; Small R; Pringle S; Hodge F; Shahid A; Gallos ID; Horne AW; Quenby S; Coomarasamy A; Mifepristone and misoprostol versus misoprostol alone for the management of missed miscarriage (MifeMiso): a randomised, double-blind, placebo-controlled trial.; Lancet (London, England); 2020; vol. 396 (no. 10253)

Study details

Country/ies where study was carried out	UK (Multi-Centre- 28 UK hospitals)
Study type	Randomised controlled trial (RCT)
Study dates	3 October 2017 - 22 July 2019
Inclusion criteria	• >16 years • Diagnosed with a missed miscarriage by pelvic ultrasound scan in the first 14 weeks of pregnancy (by last menstrual period) • Chose to have medical management of miscarriage • Willing and able to give informed consent
Exclusion criteria	• Expectant or surgical management of miscarriage • Had a diagnosis of incomplete miscarriage, life threatening bleeding, contraindications to mifepristone or misoprostol • Had participated in another trial of investigational medicinal products during their current pregnancy
Patient characteristics	Maternal age - years - mean ± standard deviation • Mifepristone plus misoprostol group: 32.8 ± 5.6 • Placebo plus misoprostol group: 32.7 ± 5.7 BMI - mean ± standard deviation • Mifepristone plus misoprostol group: 25.8 ± 5.6 • Placebo plus misoprostol group: 26.5 ± 5.5

	Previous parity - number (%) Mifepristone plus misoprostol group: • Nulliparous: 167 (47) • Parous: 190 (53) Placebo plus misoprostol group: • Nulliparous: 168 (47) • Parous: 186 (53) Gestational age - days - mean ± standard deviation • Mifepristone plus misoprostol group: 70.5 ± 13.1 • Placebo plus misoprostol group: 70.7 ± 13.8 Ethnicity - number (%) Mifepristone plus misoprostol group: • White: 296 (83) • Black: 10 (3) • Asian: 38 (11) • Other: 12 (3) Placebo plus misoprostol group: • White: 280 (79) • Black: 17 (5) • Asian: 42 (12) • Other: 15 (4)
Intervention(s)/control	• Single dose of oral mifepristone 200 mg and single dose of vaginal, oral, or sublingual misoprostol 800 µg 48 h later • Single dose of oral placebo tablet single dose of vaginal, oral, or sublingual misoprostol 800 µg 48 h later The single dose of misoprostol 800 µg could be omitted if the gestational sac had already been passed after the mifepristone or placebo tablet. If there was little or no bleeding within 48 hours, they were asked to contact the research team for consideration of a further dose of misoprostol. Participants were advised to return for a pelvic ultrasound scan 7 days after random assignment.

Duration of follow-up	1 month
Sources of funding	Research support grants from the Medical Research Council, National Institute for Health Research, Chief Scientist's Office, Wellbeing of Women, Roche Diagnostics, AstraZeneca, and Ferring, outside the submitted work.

Sample size	Randomised N= 711
	• Mifepristone plus misoprostol group: n = 357
	• Placebo plus misoprostol group: n = 354
	
	Excluded
	• Mifepristone plus misoprostol group: n = 8
	  ○ (5 lost to follow up, 3 discontinued study treatment and did not wish to attend follow-up or for further data to be collected)
	• Placebo plus misoprostol group: n = 5
	  ○ (2 lost to follow up, 3 discontinued study treatment and did not wish to attend follow-up or for further data to be collected)
	
	Completed 6-7 day follow up
	• Mifepristone plus misoprostol group: n = 349
	• Placebo plus misoprostol group: n = 349
	
	Excluded
	• Mifepristone plus misoprostol group: n = 1 missing primary outcome data
	• Placebo plus misoprostol group: n = 1 missing primary outcome data
	
	Included in data analysis of primary outcome
	• Mifepristone plus misoprostol group: n = 348
	• Placebo plus misoprostol group: n = 348

Other information	

Outcomes

Outcome	Mifepristone plus misoprostol group, , N = 357	Placebo plus misoprostol group, , N = 354
Failure to spontaneously pass the gestational sac within 7 days after random assignment Mifepristone plus misoprostol n= 348; Placebo plus misoprostol n= 348. Lower values are better No of events	n = 59 ; % = 17	n = 82 ; % = 24
Surgical intervention to complete the miscarriage up to discharge from hospital care Mifepristone plus misoprostol n= 355; Placebo plus misoprostol n= 353. Lower values are better No of events	n = 62 ; % = 17	n = 87 ; % = 25
Surgical intervention to complete the miscarriage up to and including day 7 after random assignment Mifepristone plus misoprostol n= 355; Placebo plus misoprostol n= 353. Lower values are better No of events	n = 23 ; % = 6.5	n = 19 ; % = 5.4
Surgical intervention to complete the miscarriage from after day 7 and up to discharge from hospital care Mifepristone plus misoprostol n= 355; Placebo plus misoprostol n= 353. Lower values are better No of events	n = 39 ; % = 11	n = 68 ; % = 19
Need for further doses of misoprostol within 7 days after random assignment Mifepristone plus misoprostol n= 356; Placebo plus misoprostol n= 354. Lower values are better No of events	n = 34 ; % = 10	n = 48 ; % = 14

Outcome	Mifepristone plus misoprostol group, , N = 357	Placebo plus misoprostol group, , N = 354
Need for further doses of misoprostol up to discharge Mifepristone plus misoprostol n= 357; Placebo plus misoprostol n= 354. Lower values are better No of events	n = 50 ; % = 14	n = 65 ; % = 18
Infection requiring outpatient antibiotic treatment Mifepristone plus misoprostol n= 351; Placebo plus misoprostol n= 351. Lower values are better No of events	n = 8 ; % = 2	n = 11 ; % = 3
Infection requiring inpatient antibiotic treatment Mifepristone plus misoprostol n= 351; Placebo plus misoprostol n= 351. Lower values are better No of events	n = 5 ; % = 1	n = 4 ; % = 1
Negative pregnancy test result 21 days (±2 days) after random assignment Mifepristone plus misoprostol n= 308; Placebo plus misoprostol n= 302. Higher values are better No of events	n = 237 ; % = 77	n = 230 ; % = 76
Duration of bleeding reported by woman, days Mifepristone plus misoprostol n= 326; Placebo plus misoprostol n= 330. Lower values are better Mean (SD)	16 (12.6)	16.3 (15.2)
Requirement for blood transfusion Mifepristone plus misoprostol n= 357; Placebo plus misoprostol n= 351. Lower values are better	n = 11 ; % = 3	n = 5 ; % = 1

Outcome	Mifepristone plus misoprostol group, , N = 357	Placebo plus misoprostol group, , N = 354
No of events		
Serious adverse event Women experiencing at least one serious adverse event. Collected up to discharge. Mifepristone plus misoprostol n= 357; Placebo plus misoprostol n= 354. Lower values are better **No of events**	n = 5 ; % = 1	n = 2 ; % = 1
Side effects Reported as 'adverse side effects'. Mifepristone plus misoprostol n= 357; Placebo plus misoprostol n= 354. Collected up to discharge; Total number of women experiencing at least one adverse side effect. Lower values are better No of events	n = 26 ; % = 7	n = 24 ; % = 7
Maternal death Mifepristone plus misoprostol n= 357; Placebo plus misoprostol n= 354. Lower values are better No of events	n = 0 ; % = 0	n = 0 ; % = 0

Critical appraisal – Cochrane RoB 2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Participants were randomly assigned 1:1 by a secure web-based randomisation program provided by MedSciNet. Participants, clinicians, pharmacists, trial nurses, and midwives were masked to study group*

Section	Question	Answer
		assignment throughout the trial. No differences in participant characteristic at baseline.)
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Participants, clinicians, pharmacists, trial nurses, and midwives were masked to study group assignment throughout the trial. Intention to treat analysis followed and all analyses were prespecified in a statistical analysis plan.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *[Outcome data available for most participants for all outcomes. (Failure to spontaneously pass the gestational sac within 7 days after random assignment; Surgical intervention to complete the miscarriage up to discharge from hospital care; Surgical intervention to complete the miscarriage up to and including 7 days after random assignment; Surgical intervention to complete the miscarriage from after day 7 and up to discharge; Need for further doses of misoprostol within 7 days after random assignment; Need for further doses of misoprostol up to discharge; Infection requiring outpatient antibiotic treatment; Infection requiring inpatient antibiotic treatment; Negative pregnancy test result 21 days (±2 days) after random assignment; Duration of bleeding as reported by the participant (days); Requirement for blood transfusion; Side-effects; Serious adverse events; Maternal death). Missing data stated to be less than 3%.]*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Double blind trial so participants, clinicians, pharmacists, trial nurses, and midwives were blinded.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(A pre-specified protocol was available to assess selective reporting.)*
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	No variation across outcomes

RoB: risk of bias