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Effectiveness, safety and acceptability of mifepristone compared with other interventions in reproductive-age women using emergency contraception for the prevention of pregnancy: a systematic review and meta-analysis

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ABSTRACT

Background Emergency contraception (EC) prevents pregnancy after unprotected sexual intercourse using oral medications or intrauterine devices. Comparative evidence on effectiveness and safety is essential to inform emergency contraceptive counselling.

Objectives To evaluate the effectiveness, safety and acceptability of mifepristone compared with other EC methods among reproductive-age women.

Methods We searched CENTRAL, MEDLINE, Embase, Global Index Medicus, Scopus conference abstracts, ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform through 28 February 2025. Randomised controlled trials enrolling women within 5 days of unprotected sexual intercourse and comparing mifepristone with oral EC methods (levonorgestrel (LNG), Yuzpe regimen, ulipristal acetate) or intrauterine devices (IUDs) (copper or LNG) were included. Pregnancy was the primary outcome. Risk of bias was assessed using the Risk of Bias 1 (RoB 1) tool. Meta-analyses used fixed or random-effects models and certainty of evidence was evaluated using GRADE (Grading of Recommendations Assessment, Development and Evaluation).

Results Eighty-seven trials including approximately 36 000 participants were analysed. Mifepristone reduced pregnancy risk compared with the Yuzpe regimen (risk ratio (RR) 0.14, 95% CI 0.05 to 0.41; moderate-certainty evidence). It was more effective compared with LNG with either low-dose (<25 mg; RR 0.73, 95% CI 0.59 to 0.90; high-certainty) or mid-dose (25–50 mg; RR 0.67, 95% CI 0.49 to 0.91; moderate-certainty) levels. Evidence was inconclusive regarding comparisons with the copper IUD. Mifepristone causes less nausea and vomiting than Yuzpe. Mifepristone increases the risk of delayed menses relative to both Yuzpe and LNG.

Conclusions Mifepristone is an effective emergency contraceptive, potentially more effective than commonly used oral EC methods, with a favourable side effect profile aside from delayed menstruation.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Emergency contraception (EC) is vital for preventing unintended pregnancies, with levonorgestrel, ulipristal acetate and copper intrauterine devices serving as the most common options.

⇒ Mifepristone has been used as EC for more than a decade, but evidence on its comparative efficacy against other methods and optimal dosing remains fragmented.

WHAT THIS STUDY ADDS

⇒ This review synthesises global data comparing mifepristone directly to other standard EC regimens and demonstrates that mifepristone offers a highly effective, well-tolerated alternative with clear data on side effect profiles and menstrual changes.

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HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study provides robust evidence for international bodies to update clinical guidelines and potentially expand mifepristone availability for EC use.

⇒ It highlights the need for future trials to directly compare mifepristone with ulipristal acetate, evaluate outcomes stratified by body mass index and time since intercourse, and utilise standardised reporting for adverse events and acceptability.

INTRODUCTION

Emergency contraception (EC) prevents pregnancy after unprotected sexual intercourse or contraceptive failure. Unintended pregnancy affects an estimated 121 million people worldwide[1] and is associated with substantial health and social consequences, particularly in settings with higher maternal morbidity and mortality.[2] Oral EC methods included in many clinical guidelines are levonorgestrel (LNG), ulipristal acetate (UPA) and combined oral contraceptives (the Yuzpe regimen with oestrogen and progestogens).[3 4]

Mifepristone, a progesterone receptor antagonist widely used for medication abortion, has also been studied as EC at single oral doses ranging from 10 mg to 600 mg administered within 120 hours of intercourse. Despite a large evidence base, it is approved for EC in relatively few countries (eg, China, Armenia, Russia, Ukraine)[5] and is not consistently included in global EC guidelines. Because access to the copper intrauterine device (Cu-IUD) can be limited by the need for timely clinical insertion and procedural pain control and UPA can be constrained by cost and availability,[6] additional effective oral options are important.

This review updates the mifepristone component of the 2019 Cochrane review of interventions for emergency contraception[7] to inform forthcoming international guidelines. The full Cochrane systematic review can be found in the Cochrane Database of Systematic Reviews and includes complete evidence tables and supplementary materials.

OBJECTIVE

To evaluate the effectiveness, safety and acceptability of mifepristone compared with other emergency contraceptive interventions in reproductive-age women.

METHODS

Eligibility criteria

We included randomised controlled trials (RCTs) enrolling reproductive-age women who used EC within 120 hours of unprotected sexual intercourse and comparing mifepristone with LNG, the Yuzpe regimen, UPA, Cu-IUD or LNG-IUD, or comparing different mifepristone doses. We excluded studies of induced abortion or other non-EC indications.

Search strategy and study selection

The Cochrane Fertility Regulation Group Information Specialist searched CENTRAL, MEDLINE, Embase, Global Index Medicus and Scopus conference abstracts from inception to 28 February 2025, and trial registries (ClinicalTrials.gov; WHO ICTRP). Specific search strategies are included in the online supplemental material (search strategies A-E). We screened titles/abstracts and full texts in duplicate and documented the process using PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) (online supplemental figure 1). We also reviewed reference lists, contacted experts and screened Retraction Watch.

Data extraction and risk of bias

Three review authors independently reviewed and extracted data using a standardised form. Mifepristone doses were categorised as low (<25 mg), mid (25–50 mg) and high (>50 mg). We used Cochrane Risk of Bias (RoB 1) assessments for studies from the prior review; had new studies been identified we had planned to use RoB 2, the updated risk of bias assessment tool from Cochrane. Certainty of evidence was assessed using GRADE (Grading of Recommendations Assessment, Development and Evaluation) (see the full Cochrane review for details).

Outcomes

For each outcome, the effect measures used for synthesis were prespecified. The critical outcome was pregnancy following use of mifepristone or the comparator method for EC, measured as a pregnancy rate or proportion and summarised using risk ratios (RRs) or absolute risks. Important safety and acceptability outcomes were measured as rates or proportions, including ectopic pregnancy, outcomes of pregnancies occurring after emergency contraceptive failure, adverse effects and user satisfaction; ordinal or continuous scales were used for satisfaction when reported. All trials assessed pregnancy rates after treatment, usually defined as the proportion of women with a confirmed ongoing or clinical pregnancy during follow-up. Pregnancy ascertainment was typically based on delayed menses, clinical examination and/or urine or serum human chorionic gonadotropin (hCG) testing at follow-up visits. Most studies reported menstrual change outcomes, commonly reported as timing of the next bleed relative to the expected date. "Early menses" refers to bleeding earlier than expected, while "delayed menses" refers to bleeding later than expected (definitions and thresholds varied across trials). Delayed menses can prompt pregnancy testing and may affect acceptability.

Side effects were also reported, including nausea, vomiting, dizziness, breast tenderness, abdominal pain and headache. Some studies reported a composite "any side effect" outcome, but these were inconsistently reported and highly varied. Some trials reported

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additional outcomes, including patient acceptability or satisfaction, bleeding patterns and, in the IUD studies, continuation or removal of the device.

An overview of the studies including country, participant numbers, study arms and included outcomes can be found in the Overview of Synthesis and Included Studies (OSIS) presented in online supplemental table 1 as well as in the full Cochrane review. Details related to obtaining additional data related to included studies can also be found in the full Cochrane review.

Synthesis and statistical analysis For each analysis, studies were assessed for eligibility based on intervention characteristics, comparators and outcome reporting, and were included in a specific analysis when they matched the prespecified comparison groups and outcome definitions described above.

We sought and analysed study data according to the intention-to-treat (ITT) principle. We assigned all participants to the original group to which they were allocated and reported the potential impact of missing data where information related to missing data was not available.

We calculated RRs with 95% CIs from reported study data. Pooled effects were estimated with meta-analysis when appropriate. The default model was random-effects with restricted maximum likelihood to compute between study variance and Hartung–Knapp–Sidik–Jonkman CIs. Alternative model specifications were used to account for very few studies, rare events and zero-cell counts.[8] We examined statistical heterogeneity with I^2 when estimable and also described clinical diversity across studies. Analyses were displayed using forest plots. Analyses and data presentation were all conducted using Cochrane Revman Web. Prespecified subgroup analyses included days from unprotected sexual intercourse, repeat intercourse in the same menstrual cycle and body mass index.

Patient and public involvement

Patients and consumers were not involved directly in this review, although we used core outcomes for the review that attempted to incorporate patient, consumer and end-user concerns.

Ethics approval

Ethical approval was not required for this study as it was a systematic review and meta-analysis of previously published research. The study does not involve the direct participation of human subjects or the collection of primary data.

RESULTS

Study selection and characteristics

We included 87 RCTs conducted between 1992 and 2015 (approximately 36 000 participants). Most trials (79 of 87) were conducted in China in family planning clinics or outpatient settings; four were from the UK, two from Cuba and two were multinational (including WHO 1999). Trials generally enrolled women presenting within 72 hours after a single act of unprotected sexual intercourse, with some extending to 120 hours. Comparator regimens were most commonly LNG 1.5 mg total dose (often 0.75 mg administered twice) or the Yuzpe regimen (with ethinylestradiol and a progestogen in a combined pill); two small trials compared mifepristone with Cu-IUD insertion. No trials were identified comparing mifepristone with LNG-IUD or to UPA.

Risk of bias

We reported Cochrane RoB 1 for the previously included trials. Reporting was frequently insufficient across four domains: random sequence generation and allocation concealment (selection bias), blinding (performance and detection bias) and incomplete outcome data (attrition bias). A risk of bias summary graph can be viewed in online supplemental figure 2.

Allocation

The few trials (12 trials) that provided detailed descriptions of both randomisation procedures and allocation concealment were judged to be at low risk of selection bias. Many trials reported minimal detail, resulting in judgements of unclear risk of bias. Seven trials reported power calculations to inform sample size.

Blinding

Eleven trials were described as double-blinded and one as single-blinded, but blinding procedures were not well described, contributing to uncertainty regarding performance and detection bias.

Incomplete outcome data

Two trials explicitly described their analyses as ITT analyses. Although 18 studies reported losses to follow-up or post-randomisation exclusions, many did not describe how missing data were handled or whether analyses followed ITT principles, resulting in unclear or high risk of attrition bias.

Selective reporting

To assess potential reporting bias, funnel plots were used when the analysis included more than 10 studies. There were some comparisons for which there were too few studies; therefore, funnel plots and statistical testing could not be performed.

Overall, reporting of key methodological domains was frequently insufficient, leading to widespread judgements of unclear risk of bias. Results from sensitivity analyses restricted to studies at lower risk of bias, when possible, did not produce results inconsistent with our overall synthesis.

Synthesis of Results

Results are presented in four primary Summary of Findings tables (tables 1–4): mid-dose mifepristone

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Table 1 Summary of Findings: Mid-dose mifepristone (25–50 mg) compared with levonorgestrel (LNG)

Outcomes	Risk with LNG	Risk with mid-dose mifepristone (25–50 mg)	Relative effect (95% CI)	Participants (n) (studies)	Certainty (GRADE)	Comments
Observed number of pregnancies	35 per 1000	23 per 1000 (17 to 32)	RR 0.67 (0.49 to 0.91)	6052 (27 RCTs)	Moderate*	Mifepristone likely results in a reduction in pregnancies compared with LNG
Any side effect	202 per 1000	111 per 1000 (79 to 154)	RR 0.55 (0.39 to 0.76)	4350 (17 RCTs)	Moderate*	Mifepristone likely reduces any side effect compared with LNG
Side effect: nausea	80 per 1000	65 per 1000 (45 to 94)	RR 0.81 (0.56 to 1.17)	713 (4 RCTs)	Low*†	Mifepristone may slightly reduce nausea compared with LNG
Side effect: spotting/bleeding after treatment	240 per 1000	144 per 1000 (127 to 163)	RR 0.60 (0.53 to 0.68)	6492 (15 RCTs)	Moderate*	Mifepristone likely reduces spotting/bleeding compared with LNG
Early menses	94 per 1000	67 per 1000 (46 to 97)	RR 0.71 (0.49 to 1.03)	1324 (7 RCTs)	Moderate*	Mifepristone likely results in a reduction in early menses compared with LNG
Delayed menses	108 per 1000	139 per 1000 (109 to 176)	RR 1.29 (1.01 to 1.64)	3615 (17 RCTs)	Moderate*	Mifepristone likely results in an increase in delayed menses compared with LNG

Notes: The risk in the intervention group (and its 95% CIs) 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 lies close to that of the estimate. Moderate certainty - we are moderately confident in the effect estimate; the true effect is likely close to the estimate but may be substantially different. Low certainty - our confidence is limited; the true effect may be substantially different. Very low certainty - we have very little confidence; the true effect is likely substantially different from the estimate.
Patient or population: women seeking emergency contraception. Setting: China; family planning clinics. Intervention: mid-dose mifepristone (25–50 mg). Comparison: LNG
*Downgraded one level for risk of bias given absence of information regarding important domains in most studies.
†Downgraded one level for imprecision because the 95% CI overlaps no effect and includes important benefit and important harm.
GRADE, Grading of Recommendations Assessment, Development and Evaluation; LNG, levonorgestrel; RCT, randomised controlled trial; RR, risk ratio.

(25–50 mg) versus LNG (table 1), low-dose mifepristone (<25 mg) versus LNG (table 2), high-dose mifepristone (100–600 mg) versus Yuzpe (table 3), mid-dose mifepristone (25–50 mg) versus low-dose mifepristone (<25 mg) (table 4) and mifepristone (any dose) versus Cu-IUD (online supplemental table 2) (see full Cochrane review for all detailed analyses and Summary of Findings (SoF) tables).

Effectiveness: Pregnancy

Mid-dose mifepristone (25–50 mg) versus LNG

Based on meta-analysis of 27 RCTs (n=6052), mid-dose mifepristone likely lowers the risk of pregnancy compared with LNG (RR 0.67, 95% CI 0.49 to 0.91; moderate-certainty). With these included studies, we assume a pregnancy rate of 35 per 1000 with LNG and this corresponds to 17–32 pregnancies per 1000 with mid-dose mifepristone. Considering low-dose mifepristone (<25 mg) versus LNG across 14 RCTs (n=8752), low-dose mifepristone reduced pregnancy risk compared with LNG (RR 0.73, 95% CI 0.59 to 0.90; high-certainty). Assuming 20 pregnancies per 1000 with LNG, this corresponds to 12–18 per 1000 with low-dose mifepristone.

High-dose mifepristone (100–600 mg) versus Yuzpe regimen

Three UK RCTs (n=2144) found that high-dose mifepristone (100–600 mg) likely reduces pregnancy compared with the Yuzpe regimen (RR 0.14, 95% CI 0.05 to 0.41; moderate-certainty). Assuming 25 pregnancies per 1000 with Yuzpe, this corresponds to about 1–10 per 1000 with mifepristone.

Mid-dose mifepristone (50 mg) versus Cu-IUD

Two small Chinese trials (n=395) reported zero pregnancies with Cu-IUD (0/150) and three pregnancies with 50 mg mifepristone (3/245). Certainty of the evidence was very low because of risk of bias and imprecision.

Comparative effectiveness of mifepristone dose

Mid-dose mifepristone (25–50 mg) versus low-dose mifepristone (<25 mg)

Across 26 RCTs (n=12 358), mid-dose mifepristone was associated with reduced pregnancy compared with low-dose mifepristone (RR 0.77, 95% CI 0.59 to 1.00; high-certainty). Assuming 16 pregnancies per 1000 with low-dose mifepristone, this corresponds to 10–16 per 1000 with mid-dose mifepristone.

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Table 2 Summary of Findings: Low-dose mifepristone (<25 mg) compared with levonorgestrel (LNG)

Outcomes	Risk with LNG	Risk with low-dose mifepristone (<25 mg)	Relative effect (95% CI)	Participants (n) (studies)	Certainty (GRADE)	Comments
Observed number of pregnancies	20 per 1000	15 per 1000 (12 to 18)	RR 0.73 (0.59 to 0.90)	8752 (14 RCTs)	High	Low-dose mifepristone reduces pregnancy compared with LNG
Any side effect	342 per 1000	89 per 1000 (58 to 130)	RR 0.26 (0.17 to 0.38)	609 (3 RCTs)	Moderate*	Low-dose mifepristone likely results in a large reduction in any side effect compared with LNG
Side effect: nausea	132 per 1000	127 per 1000 (111 to 144)	RR 0.96 (0.84 to 1.09)	6484 (6 RCTs)	Moderate†	Low-dose mifepristone likely results in a slight decrease in nausea compared with LNG
Side effect: vomiting	15 per 1000	18 per 1000 (12 to 26)	RR 1.16 (0.77 to 1.73)	6084 (3 RCTs)	Moderate†	Low-dose mifepristone likely results in a slight increase in vomiting compared with
Side effect: spotting/bleeding after treatment	287 per 1000	172 per 1000 (152 to 192)	RR 0.60 (0.53 to 0.67)	4696 (6 RCTs)	High	Low-dose mifepristone reduces spotting/bleeding after treatment compared with LNG
Early menses	182 per 1000	82 per 1000 (64 to 106)	RR 0.45 (0.35 to 0.58)	1898 (6 RCTs)	High	Low-dose mifepristone results in a reduction in early menses after treatment compared with LNG
Delayed menses	67 per 1000	102 per 1000 (74 to 139)	RR 1.52 (1.11 to 2.08)	7618 (10 RCTs)	High	Low-dose mifepristone results in a slight increase in delayed menses compared with LNG

Notes: 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 lies close to that of the estimate. Moderate certainty - we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate but may be substantially different. Low certainty - our confidence is limited; the true effect may be substantially different. Very low certainty - we have very little confidence; the true effect is likely to be substantially different from the estimate.
Patient or population: women seeking emergency contraception. Setting: China, UK, multinational; family planning clinics. Intervention: low-dose mifepristone (<25 mg). Comparison: LNG
*Downgraded by one level for an absence of information regarding important risk of bias domains (selection and attrition biases) in most of the studies included in the analysis.
†Downgraded by one level for imprecision because the 95% CI overlaps no effect and includes important benefit and important harm.
GRADE, Grading of Recommendations Assessment, Development and Evaluation; LNG, levonorgestrel; RCT, randomised controlled trial; RR, risk ratio.

Safety: Adverse events

Ectopic pregnancy was rare (5 events reported across all 87 studies) and risk estimates imprecise. Data on pregnancy outcomes after EC failure were limited; where reported, many participants opted for abortion.

Safety: Side effects (any side effect and specific side effects)

Mid-dose mifepristone (25–50 mg) versus LNG

Mid-dose mifepristone likely reduces the risk of "any side effect" compared with LNG (RR 0.55, 95% CI 0.39 to 0.76; 17 RCTs; n=4350; moderate-certainty). For specific symptoms, mid-dose mifepristone may slightly reduce nausea compared with LNG (RR 0.81, 95% CI 0.56 to 1.17; 4 RCTs; n=713; low-certainty). Mid-dose mifepristone likely reduces spotting/bleeding after treatment (RR 0.60, 95% CI 0.53 to 0.68; 15 RCTs; n=6492; moderate-certainty). Additional adverse effects (eg, headache, dizziness, breast tenderness, abdominal pain) were reported in some trials but were not consistently measured across studies.

Low-dose mifepristone (<25 mg) versus LNG

Low-dose mifepristone likely results in a large reduction in "any side effect" compared with lLNG (RR 0.26, 95% CI 0.17 to 0.38; 3 RCTs; n=609; moderate-certainty). For specific symptoms, low-dose mifepristone likely results in a small reduction in nausea (RR 0.96, 95% CI 0.84 to 1.09; 6 RCTs; n=6484; moderate-certainty) and likely results in a slight increase in vomiting (RR 1.16, 95% CI 0.77 to 1.73; 3 RCTs; n=6084; moderate-certainty) compared with LNG. The risk of spotting/bleeding after treatment was lower with low-dose mifepristone than LNG (RR 0.60, 95% CI 0.53 to 0.67; 6 RCTs; n=4696;

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Table 3 Summary of Findings: High-dose mifepristone (100–600 mg) compared with Yuzpe

Outcomes	Risk with Yuzpe	Risk with mifepristone (any dose)	Relative effect (95% CI)	Participants (n) (studies)	Certainty (GRADE)	Comments
Observed number of pregnancies	25 per 1000	3 per 1000 (1 to 10)	RR 0.14 (0.05 to 0.41)	2144 (3 RCTs)	Moderate*	Mifepristone likely results in a reduction in pregnancies compared with Yuzpe
Any side effect	709 per 1000	631 per 1000 (589 to 674)	RR 0.89 (0.83 to 0.95)	1693 (2 RCTs)	Moderate†	Mifepristone likely results in a large reduction in any side effect compared with Yuzpe
Side effect: nausea	424 per 1000	272 per 1000 (242 to 305)	RR 0.64 (0.57 to 0.72)	2186 (3 RCTs)	High	Mifepristone decreases nausea compared with Yuzpe
Side effect: vomiting	135 per 1000	15 per 1000 (9 to 26)	RR 0.11 (0.07 to 0.19)	2186 (3 RCTs)	High	Mifepristone decreases vomiting compared with Yuzpe
Side effect: abdominal pain	276 per 1000	210 per 1000 (168 to 262)	RR 0.76 (0.61 to 0.95)	1000 (1 RCT)	High	Mifepristone decreases abdominal pain compared with Yuzpe
Delayed menses	110 per 1000	312 per 1000 (255 to 383)	RR 2.83 (2.31 to 3.47)	1912 (3 RCTs)	High	Mifepristone results in an increase in delayed menses compared with Yuzpe

Notes: 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 lies close to that of the estimate. Moderate certainty - we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate but may be substantially different. Low certainty - our confidence is limited; the true effect may be substantially different. Very low certainty - we have very little confidence; the true effect is likely to be substantially different from the estimate.
Patient or population: women seeking emergency contraception Setting: UK; family planning clinics Intervention: mifepristone (any dose) Comparison: Yuzpe
*Downgraded by one level for imprecision given rare events.
†Downgraded by one level for inconsistency with two studies - one showing a decrease and one no effect.
GRADE, Grading of Recommendations Assessment, Development and Evaluation; LNG, levonorgestrel; RCT, randomised controlled trial; RR, risk ratio.

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Table 4 Summary of Findings: Mid-dose mifepristone (25–50 mg) compared with low-dose mifepristone (<25 mg)

Outcomes	Risk with low-dose mifepristone (<25 mg)	Risk with mid-dose mifepristone (25–50 mg)	Relative effect (95% CI)	Participants (n) (studies)	Certainty (GRADE)	Comments
Observed number of pregnancies	16 per 1000	13 per 1000 (10 to 16)	RR 0.77 (0.59 to 1.00)	120 358 (26 RCTs)	High	Mid-dose mifepristone results in a slight reduction in pregnancies compared with low-dose mifepristone
Any side effect	72 per 1000	112 per 1000 (76 to 165)	RR 1.56 (1.06 to 2.30)	2908 (12 RCTs)	Low*†	Mid-dose mifepristone may result in little to no difference in any side effect compared with low-dose mifepristone
Side effect: nausea	104 per 1000	113 per 1000 (94 to 137)	RR 1.09 (0.91 to 1.32)	7948 (13 RCTs)	High	Mid-dose mifepristone results in a slight increase in nausea compared with low-dose mifepristone
Side effect: vomiting	six per 1000	12 per 1000 (4 to 34)	RR 2.01 (0.72 to 5.57)	6082 (6 RCTs)	Moderate†	Mid-dose mifepristone likely results in an increase in vomiting compared with low-dose mifepristone
Side effect: spotting/ bleeding after treatment	69 per 1000	116 per 1000 (82 to 166)	RR 1.69 (1.19 to 2.41)	5078 (11 RCTs)	High	Mid-dose mifepristone increases the risk of spotting/bleeding after treatment compared with low-dose mifepristone
Early menses	130 per 1000	143 per 1000 (125 to 163)	RR 1.10 (0.96 to 1.25)	2579 (8 RCTs)	Low*†	Mid-dose mifepristone may result in little to no difference in early menses compared with low-dose mifepristone
Delayed menses	119 per 1000	157 per 1000 (136 to 178)	RR 1.32 (1.15 to 1.50)	11 733 (22 RCTs)	High	Mid-dose mifepristone results in a slight increase in delayed menses compared with low-dose mifepristone

Notes: 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 lies close to that of the estimate. Moderate certainty - we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate but may be substantially different. Low certainty - our confidence is limited; the true effect may be substantially different. Very low certainty - we have very little confidence; the true effect is likely to be substantially different from the estimate.
Patient or population: women seeking emergency contraception Setting: China; family planning clinics Intervention: mid-dose mifepristone (25–50 mg) Comparison: low-dose mifepristone (<25 mg)
*Downgraded by one level for an absence of information regarding important risk of bias domains (selection and attrition biases) in most of the studies included in the analysis.
†Downgraded by one level for imprecision because the 95% CI overlaps no effect and includes important benefit and important harm.
GRADE, Grading of Recommendations Assessment, Development and Evaluation; LNG, levonorgestrel; RCT, randomised controlled trial; RR, risk ratio.

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high-certainty). Across studies, other side effects (eg, headache, dizziness, fatigue, breast tenderness, abdominal pain, diarrhoea, hot flashes) were variably reported, limiting synthesis.

High-dose mifepristone (100–600 mg) versus Yuzpe regimen

Compared with the Yuzpe regimen, mifepristone likely results in a large reduction in the risk of any side effect (RR 0.89, 95% CI 0.83 to 0.95; 2 RCTs; n=1693; moderate-certainty). Mifepristone decreases nausea (RR 0.64, 95% CI 0.57 to 0.72; 3 RCTs; n=2186; high-certainty) and vomiting (RR 0.11, 95% CI 0.07 to 0.19; 3 RCTs; n=2186; high-certainty) compared with Yuzpe. In one trial (n=1000), mifepristone reduced abdominal pain compared with Yuzpe (RR 0.76, 95% CI 0.61 to 0.95; high-certainty). Other symptoms (eg, headache, breast tenderness, hot flashes, lethargy) were reported in some trials but were not consistently available across studies.

Mid-dose mifepristone (50 mg) versus Cu-IUD

One trial assessed abdominal pain. No abdominal pain events were recorded in the mifepristone group, whereas 18 events occurred among Cu-IUD users (events: 0/190 vs 18/95). A relative effect estimate could not be calculated because there were no events in the mifepristone group (1 RCT; n=285; very low-certainty evidence).

Mid-dose mifepristone (25–50 mg) versus low-dose mifepristone (<25 mg)

Compared with low-dose mifepristone, mid-dose mifepristone may result in little to no difference in any side effect reporting (RR 1.56, 95% CI 1.06 to 2.30; 12 RCTs; n=2908; low-certainty). Mid-dose mifepristone also slightly increases nausea (RR 1.09, 95% CI 0.91 to 1.32; 13 RCTs; n=7948; high-certainty) and likely increases vomiting (RR 2.01, 95% CI 0.72 to 5.57; 6 RCTs; n=6082; moderate-certainty). Mid-dose mifepristone increases spotting/bleeding after treatment (RR 1.69, 95% CI 1.19 to 2.41; 11 RCTs; n=5078; high-certainty). Other symptoms were inconsistently reported.

Safety: Effect on menses

Mid-dose mifepristone (25–50 mg) versus LNG

Compared with LNG, mid-dose mifepristone probably reduces the likelihood of early menses (RR 0.71, 95% CI 0.49 to 1.03; 7 RCTs; n=1324; moderate-certainty) and likely increases the risk of delayed menses (RR 1.29, 95% CI 1.01 to 1.64; 17 RCTs; n=3615; moderate-certainty).

Low-dose mifepristone (<25 mg) versus LNG

Low-dose mifepristone reduces the risk of early menses (RR 0.45, 95% CI 0.35 to 0.58; 6 RCTs; n=1898; high-certainty) compared with LNG and slightly increases the risk of delayed menses (RR 1.52, 95% CI 1.11 to 2.08; 10 RCTs; n=7618; high-certainty).

High dose mifepristone (100–600 mg) versus Yuzpe regimen

Higher-dose mifepristone results in an increase in delayed menses when compared with the Yuzpe regimen (RR 2.83, 95% CI 2.31 to 3.47; 3 RCTs; n=1912; high-certainty). Data on early menses were not consistently reported for this comparison.

Mid-dose mifepristone (50 mg) versus Cu-IUD

Data from one small trial suggests that mifepristone may increase delayed menses risk compared with Cu-IUD insertion (RR 4.27, 95% CI 1.56 to 11.69; 1 RCT; n=284; very low-certainty) but the evidence is very uncertain because of risk of bias and imprecision.

Mid-dose mifepristone (25–50 mg) versus low-dose mifepristone (<25 mg)

Mid-dose mifepristone may result in little to no difference in early menses compared with low-dose mifepristone (RR 1.10, 95% CI 0.96 to 1.25; 8 RCTs; n=2579; low-certainty) but slightly increases the risk of delayed menses (RR 1.32, 95% CI 1.15 to 1.50; 22 RCTs; n=11 733; high-certainty).

Acceptability: Satisfaction

Two RCTs reported satisfaction. Pooled results suggest mifepristone probably increases satisfaction compared with LNG or Yuzpe (RR 1.09, 95% CI 1.05 to 1.13; 2 RCTs; n=1205; moderate-certainty), although measurement approaches varied and follow-up was incomplete in one trial.

Subgroup comparisons of mifepristone effectiveness

Effectiveness comparisons stratified by doses compared with LNG were conducted to explore the evidence for potential differences in effectiveness by dosage. Most analyses showed no statistically significant differences, with overlapping CIs. This suggests that observed differences in effect by dose may reflect chance or clinical heterogeneity across studies. Overall, mid-dose and low-dose mifepristone were similarly effective for preventing pregnancy compared with LNG and likely have similar benefits and risks in terms of undesired effects (side effects and impact on menses).

Subgroup analyses

Four trials of mifepristone versus LNG and one Yuzpe comparison trial reported outcomes stratified by time since intercourse or repeat intercourse in the same cycle; subgroup comparisons were not possible and no clear trends were seen.

DISCUSSION

Principal findings

Across 87 RCTs, both low-dose (<25 mg) and mid-dose (25–50 mg) mifepristone reduced pregnancy risk compared with LNG, and mifepristone (100–600 mg)

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reduced pregnancy risk compared with the Yuzpe regimen. Few studies compared mifepristone EC with Cu-IUD and evidence was very uncertain. Experiencing delayed menses was more common with mifepristone than with LNG or Yuzpe and could be dose-related. Serious adverse outcomes were rare and infrequently reported.

Strengths and limitations

This review used comprehensive searches, duplicate screening, RoB 1 methods and GRADE to assess certainty. However, most evidence came from trials in China with limited reporting of randomisation and concealment, and with inconsistent measurement and reporting of adverse effects and acceptability. The geographic concentration of the studies, paired with the fact that these studies were all conducted more than a decade ago, likely limit generalisability to current populations and health systems. The risk of delayed menses may be greater with mifepristone compared with LNG but stratified analyses were limited due to the clinical diversity of the included studies, whereby factors other than the dosage could account for associations. For example, all of the Yuzpe comparisons were based on higher doses of mifepristone than the LNG comparisons, limiting strong conclusions related to mifepristone dose across all types of EC. Many trials excluded women with irregular cycles or multiple acts of intercourse, potentially limiting generalisability to all EC users. Data were insufficient to clarify effectiveness by time since intercourse beyond 72 hours, by body mass index (BMI), or among women with repeat intercourse in the same cycle. Evidence comparing mifepristone with UPA or with LNG-IUDs was absent. The lack of studies directly comparing mifepristone to UPA, which is an important and effective EC option, limits our ability to contextualise relative effectiveness and safety within current clinical practice. Our review also did not identify any perinatal or fetal harms with continued pregnancy after EC exposure, but data are limited for evaluating these types of extremely rare outcomes and appropriate study designs for assessing such outcomes remain challenging.

Comparison with other evidence

Consistent with the previous Cochrane review and other systematic reviews, mifepristone is effective as EC compared with LNG and Yuzpe,[7 9–13] and the evidence base for comparisons with other forms of EC is lacking.

Implications for clinical practice

Where available, mifepristone is an effective oral EC option and may offer advantages over LNG and Yuzpe for preventing pregnancy, with fewer acute gastrointestinal adverse effects relative to the Yuzpe regimen. Clinicians should counsel that delayed menses can occur even if the medication is working, since this may affect acceptability and can prompt pregnancy testing. When Cu-IUD insertion is feasible and acceptable, it remains a highly effective option; comparative data against mifepristone are limited.

It should be noted that although mifepristone is registered in many countries, it is primarily approved for abortion care at doses substantially higher than those evaluated for EC. Based on the findings of this review, a key priority for manufacturers and policymakers may be to improve access to mifepristone for EC, as it appears to offer greater effectiveness in preventing pregnancy than the widely available LNG.

Implications for research

Future studies should evaluate effectiveness by time since intercourse, BMI and repeat intercourse in the same cycle; compare mifepristone directly with UPA; standardise reporting of adverse effects and acceptability; and improve capture of rare harms and pregnancy outcomes after EC failure. In general, the existing evidence base would benefit from updating, with new trials conducted in more diverse populations and directly comparing mifepristone with other EC formulations, as well as comparative effectiveness studies to clarify the optimal dosage.

CONCLUSIONS

Mifepristone at low- and mid-doses is an effective emergency contraceptive. Compared with LNG, low- and mid-dose mifepristone reduce pregnancy and generally reduce some adverse effects, but experiencing delayed menses is more likely with mifepristone and appears dose-related. Higher doses of mifepristone appear to reduce pregnancy when compared with Yuzpe and likely reduce gastrointestinal symptoms. Evidence comparing mifepristone with the Cu-IUD is very limited. Further research is needed that compares mifepristone for EC with other types of EC in a range of settings, addresses optimal dosage questions, and uses standard measures of side effects and patient experience.

Additional educational resources

- World Health Organization: Emergency contraception—fact sheets and guidance [14]
- American College of Obstetricians & Gynecologists: Emergency Contraception—clinical guidance/practice bulletin [3]
- Faculty of Sexual and Reproductive Healthcare (FSRH): Emergency Contraception clinical guideline [15]

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AH and JH. SR, AH and JH carried out the data extraction. In terms of analysis and reporting, SR and JH reviewed all Risk of Bias (RoB) assessments, reviewed all analyses and study data, updated the analyses using newer methods, and performed all GRADE assessments. SR and JH wrote the initial draft of the final review with writing support from AE. AH and YC contributed to the revision of the manuscript. SR, AE and JH serve as the guarantors and are responsible for the overall content of the work. Microsoft Copilot was used to display study information in tables including theOverview of Synthesis and Included Studies (OSIS) table and to modify Cochrane output such as Risk of Bias summary graphs and Summary of Findings tables to make them adhere to BMJ formatting requirements. Microsoft Copilot was also used for editing to achieve word count limits for the abstract.

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