The efficacy of medical abortion: a meta-analysis

Authors' objectives
The authors' objective seems to be to evaluate the efficacy of medical abortion with different drug regimens and at different gestational ages.

Searching
MEDLINE was searched from 1980 to mid-1998 for studies published in English and French languages using the following search terms: 'methotrexate', 'mifepristone', 'misoprostol', 'abortion', 'first trimester', 'abortion, elective', 'abortion, medical' and 'abortifacient'. Reference lists of identified studies and book chapters were also reviewed, and authors of published clinical trials were contacted.

Study selection
Study designs of evaluations included in the review
Case series or comparative studies were included, although none compared MIF and MTX regimens.

Specific interventions included in the review
Either mifepristone (MIF, 200 to 600 mg) or methotrexate (MTX, 25 to 75 mg/m2) of body surface in combination with a prostaglandin analogue, i.e. misoprostol (MIS, 200 to 800 microg) or non-MIS (other, e.g. gemeprost, sulprostone, 9-methylene PGE-2, PGO5)). Route of administration of MIS or non-MIS analogues could be oral, intramuscular or vaginal. Route of administration of MTX could be intramuscular or oral. Regimens not using a prostaglandin analogue were excluded.

Participants included in the review
Women undergoing medical abortion.

Outcomes assessed in the review
The primary clinical outcomes were:

- successful medical abortion, defined as complete medical abortion without the need for surgery;
- incomplete abortion, defined as a partially-complete abortion requiring surgery for completion; and
- viable pregnancy, defined as a live or growing foetus, requiring surgery.

Data on complications (bleeding requiring surgical haemostasis, anaemia requiring transfusion, emergency hysterectomy, uterine infection and other) and time to abortion (less than 6 hours, 1 day, 1 week or 2 weeks) were also reviewed.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review or how many of the reviewers performed the selection.

Assessment of study quality
Four aspects of study methodology were noted: pregnancy confirmation (last menstrual period (LMP) or physical examination without other tests, versus beta-human chorionic gonadotropin (hCG) urine low sensitivity, versus beta-hCG serum or urine high sensitivity, or sonography in case of doubt), gestational dating (LMP or physical examination, versus abdominal or vaginal sonography in case of doubt, versus vaginal sonography used every time); follow-up (less than 95%, 95 to 99%, greater than or equal to 99%); and outcome measurement (undefined or history
or clinical examination, versus use of serum beta-hCG with lenient definitions of completion or use of any sonogram in case of doubt, versus universal use of vaginal sonogram or strict serum beta-hCG definitions). Details on methodology were extracted by two reviewers, one familiar with medical abortion research and one not, with authors, title, data and journal blanked out. A third reviewer reconciled differences. Data were entered onto electronic spreadsheets and accuracy verified by comparison to original studies.

Data extraction
The data were extracted by two reviewers, one familiar with medical abortion research and one not, with authors, title, data and journal blanked out. A third reviewer reconciled differences. Data were entered onto electronic spreadsheets and accuracy verified by comparison to original studies. Data were extracted according to the following categories: study design, inclusion and exclusion criteria, participant characteristics (including gestational age), criteria to define pregnancy status, regimen details, techniques and criteria to measure outcomes and complications, and results.

In publications reporting multiple regimens, e.g. different prostaglandin doses, each regimen was treated as a separate study if reporting was adequately detailed.

Methods of synthesis
How were the studies combined?
Subsets of studies were examined defined by regimen type and, where possible, gestational age (at most 49 days, 50 to 56 days, and at least 57 days). Samples with at most ten participants in a gestational age category were excluded for that category. Differences within and between subsets were tested for using a modified analysis of variance. Linear regression was also performed. All analyses used random-effects models.

How were differences between studies investigated?
Homogeneity was assessed using chi-squared tests.

Analyses were repeated for the subset of studies using the most accurate diagnostic techniques, e.g. vaginal sonogram and/or serum beta-hCG. Another analysis examined whether follow-up duration was associated with outcomes within a regimen. Subgroupings of studies were examined within each gestational age-regimen category. For MIF regimes, studies were grouped by number of doses of prostaglandin (one versus more than one) and by prostaglandin route (vaginal versus oral). Sample size and quality indicators were also examined.

Linear regression was used to assess the influence of multiple predictors, such as gestational age and regimen characteristics, across all studies.

Results of the review
Forty-four studies (54 regimen arms: 18 MIF with MIS, 13 MTX with MIS and 23 MIF with other prostaglandin analogues) involving a total of 32,667 participants.

Effect of regimen: outcomes do not vary significantly by regimen except for the highest gestational age group (at least 57 days). The three regimens have very similar success rates within the gestational age groups of at most 49 days (94 to 96%) and 50 to 56 days (91%). For gestational age of at least 57 days, MIF with MIS has a lower success rate (85%) than MIF with other agent (95%); there were no studies for MTX with MIS. Success was also similar (94 to 96%) for the studies with unspecified gestational age.

There were no significant differences between regimes for incomplete abortion rates for gestational ages of at most 49 days and 50 to 56 days. For greater than 57 days, the incomplete rate for MIF combined with MIS (10%) is significantly higher than for MIF combined with another agent (6%); similarly, the mean viable pregnancy rate is significantly higher for the MIF-MIS combination (7%) than for the MIF-other combination (0.5%). When adjusted for method of outcome determination, MIF-other combination has a significantly lower viable pregnancy rate than that for the MTX-MIS combination in the linear regression.

Effect of gestational age: for MIF-MIS, success decreases from 96% for a gestational age of at most 49 days, to 85%
for one of at least 57 days. There are similar decreases in success for the other two regimens, except that MIF-other agent has a high success rate with wide confidence intervals (CIs) for 3 studies of gestational age of at least 57 days. Incomplete and viable pregnancy rates increase as gestational age increase: for MIF-MIS, these increased from 2.9 to 10% for incomplete rates and from 1.1 to 7.2% for viable pregnancy rates.

Effect of prostaglandin analogue doses: multiple doses of MIS in the MIF-MIS regimen may be better than a single dose with higher success (p=0.06), showing higher success and lower incomplete (p=0.02) and viable pregnancy rates (p=0.02) in all gestational age categories, although not in studies with unspecified gestational age.

Effect of other regimen factors: route of prostaglandin analogue administration is a significant predictor of incomplete abortion for the MIF-MIS regimen (oral 6.4%, 95% CI: 5.3, 7.6; vaginal 2.1%, 95% CI: 0.1, 6.3, p=0.05), although this effect is impossible to separate from the number of prostaglandin analogue doses. No significant relationships were found between outcomes and dose of MIF or delay in prostaglandin analogue administration.

Effect of study characteristics: study size is not related to outcomes adjusted for gestational age, using either statistical approach. The authors found no significant relationship between method of gestational dating and success for both MIF-MIS and MTX-MIS; the analysis could not be undertaken for MIF-other studies. Methods of outcome measurement did have a significant overall effect for MIF-MIS studies in the lowest gestational age group (at most 49 days). Studies that used universal vaginal sonograms or strict serum beta-hCG definitions had success rates of 98% (95% CI: 92, 100), those that used beta-hCG with lenient definitions of completion or sonogram (if there is doubt) had success rates of 97% (95% CI: 95, 99), and those with undefined measurement method or relying on history or clinical examination had success rates of 94% (95% CI: 92, 96). The analysis could not be performed for MIF-other or MTX-MIS combinations.

The relationship between length of follow-up and outcomes was also examined for MIF-MIS; no association was found.

Delay to abortion (33 studies): for successful MIF-MIS abortions, success occurred within 6 hours of prostaglandin analogue administration for 68% of women of all gestational ages, within 1 day for 91% and within 1 week for 99%. For successful MIF-other abortions, rates were 62, 83 and 89%, respectively. For MTX-MIS abortions, no studies reported results for 4 to 6 hours and success was 65% at 1 day, 76% at 1 week and 83% at 2 weeks.

Complications: data on complications were difficult to interpret. Data on one or more complications were reported for 16 MIF-MIS studies, 20 MIF-other studies and 12 MTX-MIS studies. Surgical haemostasis was the most commonly reported (0.36 to 0.54% for MIF-MIS, 0.70 to 0.71% for MIF-other and 0.62 to 0.71% for MTX-MIS). Anaemia requiring transfusion was reported at 0.18 to 0.26% for MIF-MIS, 0.08% for MIF-other and 0.40 to 0.48% for MTX-MIS. No emergency hysterectomies were reported. Uterine infection was also reported: 0.01 to 0.03% for MIF-MIS, 0.21% for MIF-other and 0% for MTX-MIS. Other complications included two ectopic pregnancies (one each in MIF-MIS and MIF-other) and five myocardial infarctions (in MIF-other). No deaths were reported in these studies.

Authors' conclusions
Both MIF and MTX, when administered when MIS, have high levels of success at 49 days of gestation or less, but may have lower efficacy at longer gestation.

CRD commentary
The review question is not clearly stated but the inclusion criteria for studies are broad and relate to the interventions only. The literature search was restricted to MEDLINE which may have led to studies being missed, although trial authors were contacted and reference lists reviewed. Restriction to articles published in the English and French languages may also have led to studies being missed. No attempt was made to find unpublished material. Validity was assessed in terms of measurements used in the studies and in sensitivity analyses but not all aspects of validity were assessed. Some details of the review process are given. Study details are presented, although the methods of pooling may not have been appropriate, particularly given the presence of heterogeneity in most of the results (the use of a random-effects model does not explain heterogeneity), it may not have been appropriate to pool studies at all. Only case series are included in the review so comparisons between MIF-MIS and MTX-MIS are not direct comparisons.
No correction appears to have been made for use of indirect comparisons in this review.

The authors' conclusions follow from the results presented but may not be reliable given the problems noted above.

**Implications of the review for practice and research**

Practice: The authors state that because efficacy is similar, the choice between MIF-MIS and MTX-MIS can be made on other criteria such as duration (favours MIF for shorter duration) and protection against ectopic pregnancy (favours MTX). The authors also state that since outcomes worsen after 49 days, medical abortions should be started before that gestational age where possible; for gestations of 50 days or more, surgical abortion should be given greater consideration. The authors advise that use of a second dose of MIS is advisable for MIF-MIS in the event that the abortion does not occur initially.

Research: The authors state that the relative cost, serious complications and side-effects of MIF-MIS versus MTX-MIS need evaluation in randomised controlled trials.

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