Meta-analysis of 200 or 600 mg mifepristone in association with two prostaglandins for termination of early pregnancy

Lievre M, Sitruk-Ware R

CRD summary
The review found 200mg and 600mg doses of mifepristone with two prostaglandins had similar rates of complete abortion, but that substitution of 600mg with 200mg may lead to an increased continuing pregnancy rate. Given the small number of included trials of uncertain quality and uncertainties about the review process, the authors' conclusions should be treated with caution.

Authors' objectives
To evaluate the efficacy and safety of 200 and 600mg mifepristone in combination with two prostaglandins for the termination of pregnancy up to 63 days' gestation.

Searching
MEDLINE and EMBASE were searched from January 2004 to December 2005 for publications in French or English; search terms were reported. Company drug registration files and WHO source data were searched for unpublished studies. The bibliography of a relevant review in 2004 was handsearched. A more recent update search was performed, which did not identify any new studies.

Study selection
Randomised controlled trials (RCTs) of head-to-head comparisons of 200 and 600mg mifepristone in combination with prostaglandins for the termination of pregnancy up to 63 days' gestation were eligible for inclusion. The primary outcomes for the efficacy of termination of pregnancy were complete success (i.e. complete expulsion of conceptus with no need for a surgical procedure) and failure (continuing pregnancy). Data was also extracted on side effects (bleeding, pain and nausea).

The two prostaglandins used in the included trials were gemeprost (1mg vaginally) and misoprostol (400μg and 600μg orally). The range of amenorrhea in participants was from 35 to 63 days.

One reviewer performed the study selection.

Assessment of study quality
No formal validity assessment was performed, but only RCTs were included and relevant data was reported for intention-to-treat analysis and loss to follow-up.

Data extraction
The number of events and success rates were extracted and expressed as a percentage for each trial. Continuous data was extracted for fall in haemoglobin level.

One reviewer performed the data extraction.

Methods of synthesis
Studies were pooled using a fixed-effect model giving percentage differences with 95% confidence intervals (CI). Non-inferiority boundaries (to maintain a given amount of efficacy versus placebo) were set by using the boundaries for success and failure set by the regulators (when mifepristone was granted its first licence). The non-inferiority boundary for success was set at -4% and for failure set at 0.5%.

Sensitivity analyses were performed to exclude one trial with a high dose of misoprostol, to exclude trials using an intention-to-treat analysis, and to compare results for two subsets of women with amenorrhea for less than 50 days and...
50 days or more. Between trial heterogeneity was determined. The impact of the prostaglandin used was not evaluated.

A narrative synthesis was provided for adverse events due to differences in event reporting.

**Results of the review**

Four relevant RCTs were identified (n=3,482 women, range 220 to 1,589). An intention-to-treat analysis was performed in two trials. Loss to follow-up ranged from 0% to 2.6%.

Success rates ranged from 89.3 to 93.8% for 200 mg of mifepristone and 88.1 to 94.3% for 600mg of mifepristone. The rate of continuing pregnancy ranged from 0.5 to 2.8% for the 200mg dose and 0 to 1.9% for 600 mg of mifepristone. The pooled percentage difference in success for 200mg versus 600 mg dose of mifepristone was 0.4% (95% CI -1.4 to 2.3), so the 200mg dose was not inferior to the 600mg dose. The pooled percentage difference in failure for 200mg versus 600mg dose of mifepristone was 0.4% (95% CI -0.3 to 1.0) but, since the upper limit was greater than 0.5%, it was not possible to conclude that the 200mg dose was not inferior to the 600mg dose of mifepristone. The sensitivity analyses did not change the overall results and there was no evidence for heterogeneity.

No severe adverse effects were reported. Results for bleeding were inconsistent across the four trials, as were the results for nausea reported in three trials. Pain appeared to be less severe for 600mg than for 200mg dose of mifepristone, but significances were not given (three studies).

**Authors’ conclusions**

Although doses of 200mg or 600mg mifepristone with two prostaglandins probably results in similar rates of complete abortion, substitution of 600mg with 200mg may lead to an increased continuing pregnancy rate. There was no difference in adverse events between mifepristone doses.

**CRD commentary**

The review addressed a well-defined question in terms of participants, interventions, study design and relevant outcomes. Relevant sources were searched and unpublished studies considered. However, language restrictions were applied, so some relevant studies may have been missed. Publication bias was not assessed. Only one reviewer undertook study selection and another reviewer data extraction, so error and bias could not be ruled out.

Trial quality was not formally assessed, so it was not possible to assess trial quality from the limited relevant data reported. The authors did not provide any information about how statistical heterogeneity was assessed. It was not clear whether the statistical analysis performed was appropriate and uncertainties regarding the setting of non-inferiority boundaries were acknowledged by the authors.

Given the small number of included trials of uncertain quality, and uncertainties about the review process, the authors’ results should be treated with caution.

Both authors disclosed financial links with Exelgyn SA (manufacturers of mifepristone).

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

**Practice:** The authors stated that their conclusion that the use of 200mg instead of 600mg mifepristone could lead to an increased continuing pregnancy rate was of high clinical relevance, since a decision would have to be made whether or not to pursue termination of pregnancy with a surgical procedure at an advanced stage of pregnancy.

**Research:** The authors recommended large factorial RCTs comparing 200mg and 600mg doses of mifepristone, using several misoprostol regimes, in order to establish whether a more active misoprostol regime would allow the use of 200mg of mifepristone with no loss in efficacy compared with 600mg. Further research was needed to identify the optimum prostaglandin regime in conjunction with mifepristone for pregnancy termination.

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