The medical management of ectopic pregnancy: a meta-analysis comparing 'single dose' and 'multidose' regimens
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CRD summary
This review assessed single- and multidose intramuscular methotrexate regimens for the medical treatment of ectopic pregnancy. The authors concluded that methotrexate regimens have high success rates and that multidose regimens are more effective than single-dose regimens. The evidence supporting the author's conclusions is not strong.

Authors' objectives
To compare the success and safety of single- and multidose intramuscular (IM) methotrexate regimens for the treatment of ectopic pregnancy.

Searching
MEDLINE was searched from 1966 to January 2001 for studies published in English; the keywords were stated. The reference lists in identified studies were also checked.

Study selection
Study designs of evaluations included in the review
Studies with less than 10 participants were excluded. Most of the included studies were case series.

Specific interventions included in the review
Studies that used standard protocols of single-dose or multidose methotrexate regimens were eligible for inclusion. Standard regimens were 50 mg/m^2 IM methotrexate for single dose and 1 mg/kg IM methotrexate, alternating with 0.1 mg/kg leucovorin IM (with up to four daily doses of each drug), for multidose regimens. Studies that used non standard treatment protocols were excluded. In the included studies, the actual number of methotrexate doses administered was more than one for 14.5% of women managed under the single-dose protocol and more than the standard four for 6.8% of women managed under the multidose dose protocol. No studies were identified that directly compared single-dose with multidose regimens.

Participants included in the review
Studies in women with ectopic pregnancy were eligible for inclusion. Studies that specifically reported the management of women with interstitial, cervical or ovarian pregnancies were excluded.

Outcomes assessed in the review
The inclusion criteria for the outcomes were not stated. The review reported the success rate, failed management, side-effects, abdominal pain, and admission to hospital for reasons other than treatment failure. The success rate was defined as the successful resolution of the ectopic pregnancy, without surgery, regardless of how many doses of methotrexate were given. Failed management was defined as the abandonment of medical treatment in favour of surgical management. The review stated that not all women with failed medical treatment had a ruptured ectopic pregnancy.

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

Assessment of study quality
The studies were assessed and scored for completeness of data reporting, study design, completeness of reporting of diagnostic criteria for ectopic pregnancy, and inclusion and exclusion criteria. One point was awarded for each criterion...
met, giving a maximum possible score of 4 points. Studies scoring 3 or 4 points were classified as high quality. The authors did not state who performed the validity assessment.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

The data extracted for each individual participant (where possible) included the number of methotrexate doses administered, the human chorionic gonadotropin (hCG) value at the start of treatment and embryonic cardiac activity. For studies reporting only the mean and standard deviation for hCG, values for individuals were estimated assuming a normal distribution. For studies that did not report standard deviations for mean hCG values, the mean value was used for all individuals. The data were extracted on an intention-to-treat basis.

Methods of synthesis
How were the studies combined?
Regression methods were used to estimate associations between treatment protocol, failed management and the presence of side-effects. Success rates and 95% confidence intervals (CIs) were calculated as simple averages for both methotrexate regimens combined, and for the separate regimens. Odds ratios (ORs) and 95% CIs for failed management were calculated for single- versus multidose regimens. ORs and 95% CIs were also calculated after adjusting for actual hCG, estimated hCG, and estimated hCG plus embryonic cardiac activity.

How were differences between studies investigated?
An analysis of failed management was conducted for all studies, for high-quality studies only, and for studies that reported individual hCG values.

Results of the review
Twenty-six case series (1,327 women: 1,067 given the single- and 260 the multidose regimen) were included.

The overall success rate for any methotrexate regimen was 89% (1,181 out of 1,327 women).

Single-dose regimens significantly increased the failure rate compared with multidose regimens; the crude OR was 1.71 (95% CI: 1.04, 2.82). The difference was still statistically significant when only high-quality studies were included.

Increasing hCG value and the presence of foetal cardiac activity were found to be significantly associated with treatment failure (P<0.001). The difference between regimens was greater after adjusting for these variables; the adjusted OR was 4.74 (95% CI: 1.77, 12.62).

The use of single-dose regimens significantly reduced side-effects compared with multidose regimens (OR 0.44, 95% CI: 0.31, 0.63). Women reporting side-effects were more likely to have successful treatment using either regimen than women without side-effects. Overall, 36.2% of women reported side-effects such as nausea, diarrhoea, mouth sores, or elevated liver transaminases; 28.3% reported abdominal pain; and 8.8% were admitted to hospital for reasons other than treatment failure.

The results were also reported for each treatment protocol according to the actual number of doses administered.

Authors’ conclusions
The treatment of unruptured ectopic pregnancy with IM methotrexate has a high success rate. Multidose methotrexate regimens are more effective than single-dose regimens.

CRD commentary
The review question was clear in terms of the intervention and participants. The inclusion criteria were broadly defined
in terms of the outcomes and study design. By limiting the included studies to those published in English and listed in one database, the authors might have missed some relevant studies. No attempt to locate unpublished studies was reported, thus raising the possibility of publication bias. The methods used to select the studies, assess validity and extract the data were not described, so it is not known whether any efforts were made to reduce errors and bias. Validity was assessed, although there were some limitations of the criteria used; in particular, the methods used to select women for inclusion in the studies was not considered.

The analysis took some potentially confounding variables into consideration. Details of the individual studies were not adequately reported, and an examination of differences among the studies was not possible. The authors' conclusions regarding the high success rates of methotrexate came from case series whose potential for bias is unknown. In addition, there were no direct comparisons of single- and multidose regimens. Given these points, the evidence supporting the author's conclusions are not strong.

**Implications of the review for practice and research**
The authors did not state any implications for practice or further research.

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