A systematic review of single-dose intramuscular methotrexate for the treatment of ectopic pregnancy

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Authors' objectives
To determine the efficacy, side-effects and complications of single-dose intramuscular methotrexate for the primary treatment of ectopic pregnancy.

Searching
MEDLINE was searched from 1968 to 1997 inclusive for articles published in any language. The bibliographies of the identified studies were examined and the first author's bibliographic database was reviewed. The authors of relevant studies were contacted for further information about published and unpublished and/or incomplete studies.

Study selection
Study designs of evaluations included in the review
Studies in which 1 or 2 doses of methotrexate were used to treat more than 10 patients with ectopic pregnancy were included if the patients fulfilled the criteria for participation.

Individual case reports of side-effects and complications were reviewed separately.

Specific interventions included in the review
Methotrexate. The interventions included the use of 1 or 2 intramuscular doses of methotrexate (50 mg/m2).

Participants included in the review
Women with a diagnosis of ectopic pregnancy, made using a combination of serum human chorionic gonadotrophin (HCG) titres, ultrasound and/or curettage as described by Stoval et al. (see Other Publications of Related Interest no.1), with ultrasound demonstration of an ectopic pregnancy of less than 3.5 cm in the greatest dimension. The mean age of the women across studies ranged from 26.1 to 33.3 years. The mean pre-treatment HCG ranged from 1,388 to 3,950 mIU/mL.

Outcomes assessed in the review
The primary outcomes were defined as regression of HCG to nonpregnant levels after 1 or 2 intramuscular doses of methotrexate. The secondary outcomes included the mean time to resolution, and the incidence of side-effects and complications.

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 authors performed the selection.

Assessment of study quality
The quality of the studies was assessed using the modified rating system developed by Chalmers et al., which was described by Petitti et al. (see Other Publications of Related Interest no.2). The authors do not state how the papers were assessed for quality, or how many of the authors performed the quality assessment.

Data extraction
The data were independently extracted by the three authors with any differences being resolved by consensus. Data were sought on the following prespecified areas: patient demographics, treatment outcomes, side-effects and complications.
Methods of synthesis
How were the studies combined?
An estimate of the pooled results was determined using the random-effects model of DerSimonian and Laird (see Other Publications of Related Interest no.3).

How were differences between studies investigated?
Potential causes of heterogeneity were discussed, although no formal assessment was undertaken.

Results of the review
Nine studies (N=408) were used to examine the efficacy of methotrexate in ectopic pregnancy. Ten case reports of side-effects were identified.

No randomised controlled trials were identified. The data were identified prospectively in 6 of the 9 studies, retrospectively in 3 studies. Eight of the 9 identified studies included some patients treated with 2 successive doses of intramuscular methotrexate.

The proportion of patients successfully treated with 1 dose was 71% (95% confidence interval, CI: 58, 81), while the proportion successfully treated with 1 or 2 doses was 84% (95% CI: 77, 90).

The proportion of patients with side-effects was 24% (95% CI: 9, 47). The side-effects mentioned in the case studies included life-threatening neutropenia, haematosalpinx, acute abdomen after rupture of ectopic pregnancy, reversible alopecia, pelvic haematocoele, severe pneumonitis, delayed rupture and chronic ectopic pregnancy. Other side-effects reported after a single dose of methotrexate included nausea, vomiting, diarrhoea, stomatitis, elevated liver function tests, dehydration, and fatigue.

The proportion of patients with an exacerbation of pain was 40% (95% CI: 25, 57).

The proportion of patients with a ruptured ectopic pregnancy was 10% (95% CI: 7, 14).

Authors' conclusions
The pooled data showed that a single dose of intramuscular methotrexate was associated with a high failure rate. The follow-up was prolonged and there was a significant incidence of minor side-effects. Serious complications and side-effects also occurred. The use of intramuscular methotrexate should be confined to clinical trials until more evidence is obtained to support its more widespread use.

CRD commentary
Both published and unpublished studies were sought and no language restrictions were applied.

The reasons for excluding those retrieved studies that did not meet the inclusion criteria were given. Quality was assessed and details were given of the methods used to extract the data. The outcomes included the incidence of side-effects. The use of a random-effects model to estimate pooled results was appropriate in view of the wide range of outcome data. The potential advantages and disadvantages of treatment with methotrexate were discussed, as were directions for future research. More comprehensive details of the literature search would have been helpful, such as the keywords used and details of the source of the author's bibliographic database. No details were given of the methods used to select studies for inclusion or to assess quality. Although quality was assessed, details of the findings were not mentioned. Heterogeneity was not formally assessed, and although the authors commented that a wide range in the outcomes was demonstrated, no investigation of this was undertaken. The secondary outcomes included the mean time to resolution, but no results were reported. The conclusion also referred to single-dose methotrexate, but the authors reported that the majority of the identified studies (8 of the 9) included some patients treated with 2 successive doses of intramuscular methotrexate. No separate analysis appears to have been undertaken on patients who received only 1 dose of methotrexate.

The authors' conclusion that intramuscular methotrexate should be confined to clinical trials is supported by the
Implications of the review for practice and research
Practice: The authors suggest that patients should be counselled regarding the need for early presentation if an exacerbation of pain occurs, and the necessity for such patients to live close to emergency care facilities. The authors recommend these precautions in view of the unpredictable occurrence of tubal rupture up to 30 days after a single dose of methotrexate.

Research: The authors suggest that future research should include the application of more stringent inclusion and exclusion criteria to patients treated with intramuscular methotrexate, and the outcomes should cover future fertility, the incidence of side-effects, complication rates, and the overall costs. Randomised trials are also required to compare single-dose intramuscular methotrexate with laparoscopic salpingostomy, salpingectomy, and placebo or expectant management.

Bibliographic details

PubMedID
9653847

Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
Adult; Drug Administration Schedule; Female; Humans; Injections, Intramuscular; Methotrexate /administration & dosage /adverse effects; Pregnancy; Pregnancy, Ectopic /drug therapy /mortality; Pregnancy, Tubal /drug therapy /mortality; Risk Factors; Rupture, Spontaneous; Survival Analysis; Treatment Failure

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.