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Review

Multiple-dose and double-dose versus single-dose administration of methotrexate for the treatment of ectopic pregnancy: a systematic review and meta-analysis

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KEY MESSAGE

This meta-analysis compares the three protocols for the treatment of ectopic pregnancy. The aim was to explore which regimen is appropriate for patients with ectopic pregnancy. The double-dose regimen was an efficient and safe alternative to the single-dose protocol.

A B S T R A C T

In this systematic review and meta-analysis, the effectiveness and safety among different dosage of methotrexate protocols for the treatment of unruptured tubal ectopic pregnancy was evaluated. Six studies of randomized contorlled trials were identified through searches conducted on *PubMed*, *Embase* and *Cochrane Library* between January 1974 and March 2016. The overall success rate of multiple-dose protocol was similar to the single-dose protocol (RR 1.07, 95% CI 0.99 to 1.17, I^2 = 0%). The difference between double-dose and single-dose groups was not significant (RR 1.09, 95% CI 0.98 and 1.20, I^2 = 0%). The incidence of side-effects of double-dose regimen was similar with single-dose regimen. Side-effects, however, are more common in multiple-dose regimen (RR 1.64, 95% CI 1.15 to 2.34, P = 0.006, I^2 = 0%). This meta-analysis indicated that the incidence of side-effects of multiple-dose protocol was significantly higher than single-dose protocol, and the success rates between them were similar. The double-dose regimen was an efficient and safe alternative to the single-dose protocol. Further high-quality researches are needed to confirm our findings and to develop the optimal protocol.

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Introduction

Ectopic pregnancy is a gynaecologic acute abdominal disease and an important cause of maternal mortality in early pregnancy (Agdi and Tulandi, 2009). The rate of ectopic or extrauterine pregnancy is 1.3–2% (Lozeau and Potter, 2005). Methotrexate, a folinic acid antagonist, has been used as first-line therapy for haemodynamically stable patients with ectopic pregnancies (Stovall, 1995; ACOG practice bulletin. Medical management of tubal pregnancy. Number 3, December 1998. Clinical management guidelines for obstetrician gynecologists. American College of Obstetricians and Gynecologists, 1999; Lipscomb et al., 2000). Systemic methotrexate (MTX), involving multiple-dose, single-dose and double-dose protocols, have been reported for the treatment of haemodynamically stable ectopic pregnancy (American College of Obstetricians and Gynecologists, 2008). Consensus has not been achieved, however, on which protocol is optimal (Hajenius et al., 2007).

The multiple-dose regimen involves the administration of four intramuscular methotrexate doses alternating with intramuscular leucovorin rescue factor (Lipscomb et al., 2000). The single-dose protocol includes only a one-time administration of intramuscular methotrexate, then the serum HCG values are observed on day 4 and day 7; if the serum HCG level reduction is less than 15%, a second dose of methotrexate is required (Stovall et al., 1991; ACOG practice bulletin. Medical management of tubal pregnancy. Number 3, December 1998. Clinical management guidelines for obstetrician gynecologists. American College of Obstetricians and Gynecologists, 1999). This protocol has been developed in an attempt to reduce the incidence of side-effects after a multiple-dosing regimen, eliminating the need of leucovorin rescue factor, and to increase the convenience of administration (Barnhart et al., 2003). The double-dose protocol (also called 'two-dose' protocol) includes the administration of two methotrexate doses on day 0 and day 4, which was developed in an attempt to combine the efficacy and safety of the multiple-dose and single-dose regimens (Barnhart et al., 2007).

No meta-analysis, however, has compared the treatment success rates and side-effects rates of the three protocols. Therefore, we conducted this meta-analysis to explore which regimen is appropriate for patients with ectopic pregnancy.

Materials and methods

Study design

This systematic review and meta-analysis strictly followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines 2009 (Altman et al., 2009).

Search strategy

Relevant studies were identified by searching *PubMed*, *Embase* and *Cochrane library* for studies published between January 1974 and March 2016. The following key words were used: 'methotrexate' or 'MTX', 'ectopic pregnancy' or 'tubal pregnancy' and 'dose'. The reference lists of all publications were hand-searched to identify missing relevant publications. Two authors (CY, YG) independently conducted the search, and reviewed titles, abstracts and full manuscripts.

Table 1 – Study eligibilty criteria.

Population	Patients diagnosed with ectopic pregnancy.
Intervention	Standard single-, double- or multiple-dose methotrexate protocols applied for the treatment of ectopic pregnancy.
Comparison	Double-dose versus single-dose methotrexate protocols; multiple-dose versus single-dose methotrexate protocols.
Outcomes	Risk ratios of overall success events and side-effects.
Study design	Randomized control trials.

Eligibility criteria

The study selection criteria are presented in **Table 1**.

Study selection

Trials were selected according to the eligibility criteria. Only studies with randomized design were included. The meeting abstracts fulfilling the criteria were also included. Case series, retrospective or non-randomized trials were excluded. This process was carried out by two authors independently.

Data extraction

Two authors independently extracted the following data from each included study: first author's last name, year of publication, number of patients, size of the ectopic pregnancy, serum HCG concentration, presence or absence of fetal cardiac activity, overall success rate and incidence of side-effect. Any disagreements were resolved by consultation with a third author.

Assessing the risk of bias and grading the quality of evidence

For randomized controlled trials, the Cochrane Collaboration's tool was used to assess the risk of bias (Higgins and Green, 2011), and the GRADE system was used to assess the grades of evidence (Atkins et al, 2004). The assessment for the risk of bias was strictly conducted according to the guidelines in the Cochrane handbook. Two authors independently reviewed the studies and assigned a value of 'low', 'uncertain' or 'high' to six domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias.

The GRADE system identified the following four grades to rate the quality of evidence (Schuiiemann and Oxman, 2009): (1) high: further researches are unlikely to change the estimate of the effects; (2) moderate: further researches are likely to influence the estimate of the effects; (3) low: further researches are very likely to change the estimate of the effects; and (4) very low: the estimate of the effects is very uncertain.

Outcome measures

The primary outcome measure was the treatment success, which was defined as a higher than 15% reduction of serum HCG between day 4 and day 7 (single- and double-dose group). For multiple-dose protocol, the treatment success was defined as a 15% decrease of serum HCG in 48 h or after administration of four doses of MTX. The above definitions were regarded as treatment success whether or not a

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