

Systemic methotrexate in the management of ectopic pregnancy and pregnancy of unknown location

Dear Editor,

Ectopic pregnancy (EP) occurs in 2% of all spontaneous conceptions. It can be a life-threatening condition and is the most common cause of mortality during the first trimester of pregnancy, contributing to 7% of all pregnancy-related deaths.^{1,2} The risk factors for EP include tubal damage following surgery or infection, smoking, and in vitro fertilisation. The fallopian tube is the most common location of ectopic implantation, accounting for more than 90% of cases.

EP can be managed surgically, medically, and occasionally by expectant management. Medical management of EP has grown in popularity, and several observational studies have reported success rates with a single dose of systemic methotrexate (MTX) in the range of 65–95%, with 3–27% of women requiring a second dose.¹

Pregnancy of unknown location (PUL) is defined as the condition when there is no evidence of an intra-uterine pregnancy, extra-uterine pregnancy or retained products of conception on a transvaginal ultrasound scan despite a positive pregnancy test. A single dose of MTX 50 mg/m² has been used successfully in women who present with symptomatic persistent PUL, leading to a subsequent resolution of serum β -human chorionic gonadotropin (hCG) levels.

We conducted a review of the medical management of EP and PUL with MTX at KK Women's and Children's Hospital, Singapore. Also examined are predictive factors for its success rate, efficacy of MTX, the need for a second dose of MTX, and the need for surgery.

This single-centre study included women with a diagnosis of EP or PUL from January to December 2019. Per institutional guidelines, the inclusion criteria for medical management of EP were haemodynamic stability, non-acute abdomen on clinical examination, β -hCG levels <5000 IU/L, tubal or adnexal mass <2 cm, and absence of fetal cardiac activity.

These women were followed up with serum β -hCG levels on day 5, day 12 and weekly thereafter until serum β -hCG levels fall below 25 IU/L. Treatment success was defined as the resolution of the serum β -hCG level to <25 IU/L. Treatment failure was defined as the need for surgical intervention. The need for a second MTX injection was not considered a treatment failure.

A total of 135 patients were included in the final analysis. Among them, 126 patients received 1 dose of MTX, while 9 patients required a second dose. The overall success rate of medical management with MTX for EP was 73.3% after 1 dose and 77% after including patients who received 2 doses of MTX (Fig. 1). The success rate of medical management for PUL was 100% (n=11) and that for fallopian tube EP was 76% (n=91/120). The overall success rate for non-tubal EPs was 50% (n=4). A total of 31 patients (23%) in our study had failure of treatment for their EPs with MTX. Among them, 27 patients had 1 dose of MTX, while 4 patients received 2 doses of MTX.

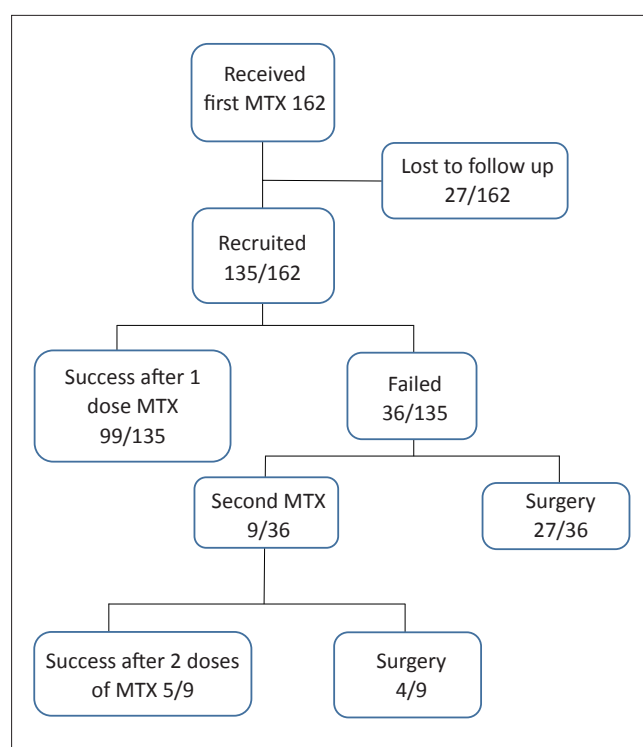


Fig. 1. Flowchart of systemic methotrexate (MTX) and success rate.

The success rate of MTX treatment was related to the initial β -hCG levels. When the initial β -hCG level was less than 1500 IU/L, the success rate was 88% (n=86/98) ($P<0.0001$); when the initial β -hCG level was between 1500–3000 IU/L, the success rate was 67% (n=14/21). When the initial β -hCG level ranged 3000–4000 IU/L, the success rate was 50% (n=3/6); when the initial

β -hCG level was between 4000–5000 IU/L, the success rate was 14% ($n=1/7$). Women should be informed of the reduced success rate with a high initial serum β -hCG level when discussing treatment options, and caution should be exercised in this group of women.

In our series, 23% (31/135) required surgery. Of these, majority ($n=29$) were tubal EPs and 2 were non-tubal EPs (1 scar EP and 1 interstitial EP). In this group, 17 patients presented as an emergency with either abdominal pain or vaginal bleeding necessitating an emergency surgery. The rest ($n=14$) underwent surgery for persistently high β hCG levels.

In our study population, the overall MTX treatment success rate was 88% when the initial β -hCG level was <1500 IU/L. The multivariate analysis that looked into various parameters in our study showed that only β -hCG level <1500 IU/L on D1 was a statistically significant predictive factor of MTX treatment success ($P<0.0001$). Other studies conducted by Potter, Kirk and Dudley et al. also reported that treatment success rates are higher with lower β -hCG levels, and the success rates were 81–98% if the serum β -hCG levels were <1000 IU/L, compared with 38% if β -hCG levels were >5000 IU/L.³⁻⁵

There was no reported success of MTX when the initial β -hCG level was over 5000 IU/L in our study. This is in keeping with a previous systematic review of 503 patients that showed a statistically significant increase in failure rates when initial β -hCG levels were >5000 IU/L compared with those who had initial levels of <5000 IU/L (odds ratio 5.5, 95% confidence interval 3.0–9.8).⁶ Therefore, women with an initial serum β -hCG level of >5000 IU/L should be offered surgery as the first line management option; this is in keeping with the 2019 NICE guidelines.⁷

In conclusion, our review showed that the overall success rate for the medical management of EP and PUL with MTX was 77% with no serious treatment related morbidity. Therefore, a systemic MTX treatment for EP and PUL in a carefully selected group of women is a safe alternative to surgery. Our study emphasises that the initial serum β -hCG level <1500 IU/L is the

single most important prognostic indicator of treatment success. Women desirous of the medical management of their EP or PUL with initial β -hCG level >3000 IU/L should be thoroughly counselled. They must also be informed of the risks, and estimated duration and number of follow-ups. Surgery should be offered as the first line with β -hCG levels >5000 IU/L.

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