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REVIEW PAPER

Fertility after methotrexate treatment for ectopic pregnancy: a narrative review

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Abstract

Background: Ectopic pregnancy (EP) occurs in up to 2% of all pregnancies, and its most common location is the fallopian tube. Treatment options include methotrexate (MTX), surgery and expectant management.
Material and methods: This review synthesizes the most important studies investigating the effect of MTX therapy for EP on subsequent female fertility.
Results: MTX treatment for EP does not seem to influence ovarian reserve. There are few studies and multiple discrepancies regarding tubal patency after MTX treatment. The pooled long-term rate of intrauterine pregnancies after MTX treatment was 69.6%, and of recurrent EP, 10.1%. MTX administered for EP treatment has a similar or better effect on subsequent fertility compared to surgery or expectant management.
Conclusions: MTX administration for EP gives equal or better outcomes in terms of subsequent fertility compared to other treatment methods. However, the chances of pregnancy are lower than in the general population. Due to the small number of RCTs and studies with long-term follow-up, future research is needed to provide definitive conclusions.
Keywords: methotrexate, fertility, ectopic pregnancy, pregnancy, birth rate

Introduction

Ectopic pregnancy (EP) occurs when a developing blastocyst implants outside of the uterine cavity. EP affects 1–2% of pregnancies. The most common location of EP is the fallopian tube (95%). Other positions include interstitial 2–4%, ovarian 3%, cervical 1%, or heterotopic 1–3% (concurrent

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presence of intrauterine and ectopic pregnancy) [1]. EP is responsible for 3–10% of pregnancy-related deaths, with the mortality rate remaining relatively stable over the years [1–3].

The combination of advanced ultrasound imaging and serial measurements of serum beta-human chorionic gonadotropin (b-hCG) allows 95–99% of cases of EP to be diagnosed [4]. Other biomarkers, such as activin-A, activin-B, activin-AB, follistatin, disintegrin and metalloprotease protein-12 (ADAM-12), Pregnancy-Associated Plasma Protein A (PAPP-A), Vascular Endothelial Growth Factor A (VEGF-A), Placental Growth Factor (PIGF), miRNAs, pregnancy-specific beta-1-glycoprotein 9 (PSG9), 3 (PSG3) and 11 (PSG11), heat-shock proteins 10 (HSP-10) and 27 (HSP-27), are the subject of intense research since their serum levels may help to distinguish a tubal EP from an early intrauterine pregnancy (IUP), or to predict EP treatment success [5–13].

There are several treatment options depending on the symptoms, the general condition, the b-hCG serum level, the presence of a viable embryo, and the diameter of the gestational sac [14]. In stable patients, non-symptomatic ones or those with mild symptoms, methotrexate (MTX) administration is a widely recognized and safe method. MTX in the treatment of EP can be administered intravenously or intramuscularly, using a one- or multi-dose protocol [1,15]. Medical treatment with MTX has good outcomes in cases of small masses (up to 3.5–4 cm), the absence of a foetal heart rate and/or relatively low b-hCG levels (up to 5000 mIU/ml) [16–18]. In patients with larger masses or very high b-hCG levels, surgical treatment with salpingostomy or salpingectomy might be needed. Surgical management is the treatment of choice in unstable patients, after ineffective MTX therapy, in women with ovarian pregnancy or those who do not accept other methods (MTX or expectant approach), or a prolonged stay in hospital, as in the case of MTX administration for tubal EP [19,20]. There are no treatment guidelines for interstitial EP or cervical pregnancy: they can be treated by administering MTX (sometimes directly into the gestational sac), surgery, or a combination of both [21–26]. The expectant approach can have a high success rate in women with tubal EP and low serum hCG levels [4,27–29].

EP is not only a life-threatening condition, but it can also affect the subsequent fertility of women trying to conceive. According to studies with long follow-up, previous EP increases the risk of recurrent EP up to 18.5% [30,31]. A large study based on the Danish national registry with follow-up of over 30 years shows that EP in the first pregnancy increases risk of further EP 4.7 times, and that EP in the first pregnancy reduces the subsequent birth rate compared to women with a normal first pregnancy, first pregnancy with a miscarriage, with an induced abortion or no previous pregnancy [32].

One of the possible mechanisms of compromised fertility after EP might be related to the chosen treatment. However, the data currently available do not provide a unanimous conclusion about the influence of medical and surgical treatment of EP on subsequent fertility. This review focuses on synthesizing data on the impact of MTX therapy for EP on subsequent fertility, with special consideration for spontaneous intrauterine pregnancy and/or birth rates.

MTX vs pregnancy: risks and timing

MTX is an antimetabolite of folic acid with proven teratogenic activity in humans and other mammals [33,34]. In the case of foetal exposure to MTX in the period of organogenesis, it can cause skull anomalies, facial dysmorphisms, cleft palate, limb abnormalities, cardiac malformations, and encephalic or neural tube defects [35]. The elimination half-life of MTX is 3–15 hours, depending on the dose, and 90% of its metabolites are eliminated in urine within 24 hours [36]. Some sources indicated the presence of MTX in liver tissues 116 days after exposure [37]. On the basis of reported MTX embryopathy and teratogenic effects of MTX in animal models, the manufacturers and scientific societies recommend avoiding pregnancy during and up to six months after exposure to MTX [16,34,38]. However, pregnancies with low rates of miscarriage or other complications have also been reported in women who conceived while receiving treatment with MTX [39–42]. Similarly, reassuring results were reported in women who became pregnant shortly after treatment of EP with MTX [43]. The authors compared foetal malformation and adverse outcome rates in pregnancies that occurred within the first six months after the last MTX treatment, and concluded that the time interval since the last MTX treatment had no effect on the outcome of the pregnancy that followed it.

MTX in the treatment of EP: influence on ovarian reserve

Most published data indicate that MTX used as a treatment for EP does not influence ovarian reserve measured in the levels of follicle-stimulating hormone (FSH) and antral follicle count (AFC), independently of the number of administered doses [44–46]. The study by Zargar et al. reported that MTX administration had no negative impact on ovarian reserve measured in levels of FSH, anti-müllerian hormone (AMH), and AFC eight weeks after the last dose of MTX [47]. Sahin et al. demonstrated that neither MTX nor MTX in association with salpingectomy affected AMH level three months after treatment of EP, although there was a temporary AMH decrease at one month in patients undergoing combined medical and surgical treatment [46]. Another recent study showed that there were no significant changes in

AMH levels one week after EP treatment with MTX compared to pre-treatment levels, both in single- and multi-dose groups [48]. Despite no significant change observed in AMH in the whole cohort within three to six months after MTX administration, the study by Çetin et al. also analyzed separately those patients with an increase vs a decrease in serum AMH level in the same time interval [49]. In both groups, the mean AMH change from pre- to post-treatment level was statistically significant. Moreover, the group exhibiting AMH increase comprised significantly more patients with a history of polycystic ovary syndrome (PCOS) and with a polycystic ovary morphology in the ultrasound. This raises the question of the effects of MTX on ovarian reserve in the general population. Therefore, in future studies it might be beneficial to analyze the influence of MTX on ovarian reserve independently for patients with and without PCOS.

MTX in the treatment of EP: influence on tubal patency

Patent tubes and ovarian reserve are important factors determining the success of future pregnancies. The mechanism in which MTX could influence tubal patency is unclear. Nevertheless, tubal patency after treatment of EP with MTX has been examined in multiple studies. A recent meta-analysis by Long et al. includes two randomized clinical trials (RCTs) comparing tubal patency after salpingostomy versus single-dose MTX for tubal EP [50–52]. It concluded that there was no difference between the two treatments. Tubal patency rates after MTX were 55% (23/42 patients) [52] and 65% (8/13 patients), respectively [50]. Another RCT by Khani et al. compared single-dose MTX, laparoscopic salpingostomy and open salpingostomy. Tubal patency rate was evaluated with hysterosalpingography at three months and was comparable between the treatments, with a rate of 91% in the MTX group (30/33 patients) [53]. A study by Melcer et al. used hysterosalpingo-foam sonography to evaluate tubal patency in patients with a history of MTX treatment for EP. It demonstrated a tubal patency rate of 60% (24/40 patients), with 15% presenting with hydrosalpinx and 25% with tube obstruction [54]. In the context of discrepancies in tubal patency rates, future studies are needed to provide a definitive conclusion.

MTX in the treatment of EP: future IUP and recurrent EP (REP)

Most studies that evaluate the effect of EP treatment on subsequent fertility compare surgical versus pharmacological treatments. In 2023, Hao et al. conducted a meta-analysis of 20 articles published between 1999 and 2022, with a total of 3530 women treated for EP, and 1023/3530 treated with MTX [55]. The primary outcomes of the study corresponded to the frequently

asked questions from the patients with EP: "Can I get pregnant successfully?" and "What is the risk of recurrence?". The follow-up period differed between these studies and ranged from 1 to15 years. Within this time period, 712 (69.6%) women conceived naturally and had an IUP. However, it should be taken into consideration that the follow-up times in some studies were relatively short (one year in three studies, one and a half years in two studies and two years in four studies), so the real rate of subsequent IUPs may be even higher. The pooled REP rate was 10.1% (75/739 patients).

As for the clinical studies that were not included in the this meta-analysis, Wyroba et al. reported that 61.5% (16/26) of patients who attempted to conceive after MTX treatment presented with successful pregnancy, resulting in live births and newborns with no congenital defects. The average time to pregnancy was 14.9 months (SD±10.9), with the first pregnancy after six months, which might be related to the received medical advice to avoid a pregnancy within three to six months after MTX treatment [56]. Reis et al. howed that 49.1% (79/161) of nulliparous patients treated with MTX gave birth within two years, and 6.8% (11/161) suffered from REP [57]. Khalil et al. reported that 54.5% of women got pregnant and gave birth to a healthy baby after MTX treatment, while 22.7% experienced a miscarriage and 13.6% an REP; the length of follow-up was not clearly reported [58]. The study by Mackenzie et al. reported follow-up data at 12 months from an RCT comparing MTX with gefitinib vs MTX with a placebo for EP treatment. Within this period, 53% (149/283) of women reported pregnancy; amongst them, 65% (93/142) delivered live babies, 40% (55/136) experienced a miscarriage and 17% (22/131), a REP [59].

MTX versus other treatments of EP

The meta-analysis by Hao et al. identified 20 studies that compared MTX and surgery, eight studies that compared MTX and salpingostomy, and six studies that compared MTX and salpingectomy [55]. They demonstrated that MTX treatment resulted in better subsequent fertility in terms of IUP rate when compared to surgery in general (OR=1.52, CI: 1.20–1.92), as well as when compared to salpingectomy (OR=1.61, 95% CI:1.52–2.93). However, there was no significant difference in IUP rate when comparing MTX and salpingostomy. As for the rate of subsequent REP, there was no significant difference in either of the comparisons. Therefore, Hao et al. concluded that future fertility after EP treatment is less compromised by pharmacological treatment than by surgery, and, if an operation is needed, salpingostomy is a better choice. It is also worth noting that the necessity of MTX use was not associated with worse subsequent fertility, since the odds of subsequent

IUP were similar in MTX and expectant management groups. A more recent study from 2024 described similar results, showing that in a two-year follow-up there was no significant difference in the rate of viable pregnancies between MTX and expectant management, but that there were significantly more pregnancies in the MTX group compared to the surgery group [60]. However, some studies report equally favourable outcomes of surgery and MTX in the treatment of EP. Dur et al. showed that both live birth (51.6% vs 44.6%) and REP (2.3% vs 1.4%) rates were not statistically different between the group treated with MTX versus the group treated with salpingectomy [61]. In the study by Alanwar et al., during the four-year follow-up, 62.5% (15/24) of patients treated with MTX presented with an intrauterine viable pregnancy, while in the case of those who had undergone surgery, this figure was 84.6% (22/26) (the difference was not statistically significant). REP occurred in 12.5% (3/24) of patients in the MTX group, and in none of the patients in the surgery group (the difference was not statistically significant) [62]. Finally, a study by Zieba et al. found similar live birth rates of 40–43.5% for patients treated previously with MTX, salpingotomy or salpingectomy, and a significantly better rate of 50% for patients treated with expectant management; however, this group comprised only eight patients and as such was much smaller than other treatment groups [19].

Conclusions

Contrary to previous beliefs, some clinical studies suggest that the time since the last MTX treatment of EP may have no effect on the outcomes of the subsequent pregnancy. EP treatment with MTX does not seem to influence the ovarian reserve, evaluated with FSH, AMH and AFC. However, future studies are needed to ensure a separate analysis for patients with normal versus polycystic ovarian morphology and function. There are few studies and multiple discrepancies regarding tubal patency after MTX treatment. Future studies are required to provide definitive conclusions. According to the literature, 84% of couples trying to conceive get pregnant within the first 12 months [(63]. Fertility after MTX treatment of EP was reported as a pooled 69.6% rate of IUP, according to a meta-analysis of over one thousand patients with follow-ups from 1 to 15 years [55]. In the same study, the pooled REP rate was 10.1%. Not taking into consideration the patients' procreative plans (in other words, including the patients who are not trying to conceive) and reporting outcomes from short follow-ups may provide a false image of birth rates after MTX treatment. MTX administered for EP treatment has a similar or better effect on subsequent fertility compared to surgery or expectant management.

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