



METHOTREXATE TREATMENT OF ECTOPIC TUBAL PREGNANCY

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SUMMARY – Aim: This paper presents the results of our research and compares them with other recent papers on this topic.

Methods: This study included 82 patients with ectopic tubal pregnancy who were hospitalized and treated in the Clinic for Gynecology and Obstetrics, Sestre milosrdnice University Hospital Center from November 2022 to November 2023. The patients' data were compared according to the treatment method, the initial level of serum human chorionic gonadotropin (hCG), and basic demographic and maternal parameters.

Results: Laparoscopic salpingectomy was used to treat 58 (70.73%) patients, 15 (18.29%) patients were treated with methotrexate, and in three (3.65%) patients who received methotrexate the treatment was unsuccessful and surgery was required. The serum hCG level in all patients treated with methotrexate was below 2000 IU/L. Of the 82 included patients, mostly aged 30-39, 42 were nulliparous and 71 were able to conceive spontaneously.

Conclusion: Our success rate of treatment with methotrexate roughly follows world trends. The serum hCG level is an essential but not an exclusive criterion for the decision on treatment. Further research is needed on how to treat patients with a serum hCG level between 2000 and 5000 IU/L with no significant clinical symptoms and unremarkable ultrasound findings.

Keywords: *Ectopic pregnancy; Methotrexate; hCG; Expectant management*

Introduction

Ectopic pregnancy implies any nidation of the embryo outside its physiological seat: the uterine cavity. Most ectopic pregnancies (95-98%) are tubal, i.e. located in the fallopian tube¹. Other localizations constitute a significantly smaller number². The incidence of ectopic pregnancies has increased over the last years³. About 2% of all pregnancies in the USA are ectopic^{3,4}, while in the United Kingdom, the estimated incidence is 11.1 per 1,000 reported pregnancies⁵. Well-known

risk factors for the development of ectopic pregnancy are previous operations on the fallopian tubes, a pathology of the fallopian tubes, previous ectopic pregnancy and the use of an intrauterine device^{6,7}. The risks associated with increasing the incidence of ectopic

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pregnancy are pelvic inflammatory diseases (mainly *Chlamydia trachomatis* infections), age (40 years and older), smoking, infertility and assisted reproductive technology (ART) procedures⁸⁻¹⁰. The most commonly used treatment method for ectopic tubal pregnancy is surgery; most often, laparoscopic salpingectomy or, much less frequently, salpingostomy, while the open approach is rare today¹¹. Another modality is medical treatment with methotrexate, either in a single-dose or multi-dose protocol. The single-dose protocol is most common due to fewer adverse effects and better patient cooperation^{12,13}. An additional option is the expectant approach: it is possible in fewer patients, but has nonetheless become an interesting and more actively researched topic¹⁴. The decision on the treatment method depends on several factors: the patient's clinical condition, ultrasound findings, serum hCG levels and the possibility of patient follow-up^{6,15-17}. For methotrexate treatment, clinical presentation (a clinically stable and pain-free patient) and serum hCG levels are the main factors and predictors of a successful treatment process. It is generally accepted that the lower the serum hCG (< 1500 IU/L), the better the outcome of treatment^{12,18,19}. In this paper, we will present our results and reflect on recent papers.

Methods

A total of 82 patients with ectopic tubal pregnancy were hospitalized and treated at Sestre milosrdnice University Hospital Center, Clinic for Women's Diseases and Obstetrics, Institute for Minimally Invasive Gynecology in the period of one year (November 2022 to November 2023). The patients' data were collected retrospectively. The patients were classified into four groups, according to treatment method: surgical treatment (laparoscopic salpingectomy), a single-dose regimen of methotrexate*, the expectant approach, and the last group included patients who were initially treated with methotrexate but, due to treatment failure, subsequently underwent laparoscopy. Patients who received an additional dose of methotrexate were not included in the latter group because their treatment was not considered a failure. Serum hCG levels, the age of the patients, their parity and the onset of pregnancy were compared between the mentioned groups.

*The standard dose of methotrexate was calculated according to the following formula: 50 mg/m² body surface or 1 mg/kg body weight¹³. All doses of methotrexate for patients in this research were calculated using this formula.

The criteria for the decision on methotrexate treatment were clinical presentation, serum hCG levels, ultrasound findings and the possibility of patient cooperation^{15,16}. The serum hCG level was an essential, but not an exclusive criterion. All our patients treated with methotrexate had serum hCG levels below 2000 IU/L. Clinical presentation, i.e. a patient without significant pain, ultrasound findings (an adnexal mass smaller than 35 mm without visible embryocardia and no signs of rupture of the adnexal mass, i.e. no free fluid in the pouch of Douglas) and the definitive exclusion of intrauterine pregnancy were other applied criteria.

Statistical data analysis was performed in the GraphPad Prism program (version 8.4.3.686, GraphPad Software, USA). The comparison between individual groups was made with the help of a 2×2 contingency table and Fisher's exact test, where the level of statistical significance was $P < 0.05$.

Results

As shown in Table 1, out of the 82 included patients, 58 (70.73%) were treated surgically, 15 (18.29%) with a single dose of methotrexate, six (7.31%) ectopic pregnancies resolved without any procedure and three (3.65%) patients underwent laparoscopy after unsuccessful methotrexate therapy. As expected, out of the total number of patients, the number of those who underwent surgery was statistically significantly higher than for all other treatment methods. Likewise, a statistically significantly higher number of women received only a single dose of methotrexate compared to those who later underwent surgery ($P = 0.0047$).

Regarding the patients' age, most patients were 30-39 (57.32%) years of age. In the surgically treated group, there was a statistically significantly higher number of those in the 30-39 age range compared to the younger age group ($P = 0.0003$). At the same time, a considerably smaller number of patients was surgically treated in the group of women older than 40 ($P < 0.0001$), which is expected given the substantially lower number of

Table 1. Demographic and material data

		Method of treatment					
		Laparoscopy (LPSC)	Methotrexate (MTX)	Expectant approach	MTX/LPSC		
Total number of patients		82	58 (70.73%)	15 (18.29%)	6 (7.31%)	3 (3.65%)	
P-values	LPSC vs MTX	LPSC vs expectant	LPSC vs MTX/LPSC	MTX vs expectant	MTX vs MTX/LPSC	Expectant vs MTX/LPSC	
	<0.0001	<0.0001	<0.0001	0.0596	0.0047	0.3252	
	Patients' age						
	20-29 years	23 (28%)	14 (24%)	6 (40%)	2 (33.33%)	1 (33.33%)	
	30-39 years	47 (57.32)	34 (58.62%)	7 (46.66%)	4 (66.66%)	2 (33.33%)	
>40 years	12 (14.63)	10 (17.24%)	2 (13.33%)	0	0		
P-values		LPSC	MTX	Expectant approach	MTX/LPSC		
	20-29 vs 30-39	0.0003	>0.9999	0.5671	>0.9999		
	20-29 vs >40	0.4923	0.2148				
	30-39 vs >40	<0.0001	0.1086				
Parity	0 births	42 (51.22%)	31 (53.44%)	6 (40%)	4 (66.66%)	1 (33.33%)	
	1-2 births	39 (47.56 %)	27 (46.55%)	8 (53.33%)	2 (33.33%)	2 (66.66%)	
	3 or more	1 (1.22%)	0	1 (13.33%)	0	0	
P-values		LPSC vs MTX	LPSC vs expectant	LPSC vs MTX/LPSC	MTX vs expectant	MTX vs MTX/LPSC	Expectant vs MTX/LPSC
	0 births	<0.0001	<0.0001	<0.0001	0.7379	0.1092	0.3597
	1-2 births	<0.0001	<0.0001	<0.0001	0.0866	0.0866	>0.9999
Spontaneous pregnancy/Assisted reproductive technology (ART)							
Spontaneous		71 (86.59%)	49 (84.48%)	15	5 (83.33%)	2 (66.66%)	
ART		11 (13.41%)	9 (15.51%)	0	1 (16.66%)	1 (33.33%)	

LPSC = laparoscopy; MTX = methotrexate; MTX/LPSC = failed methotrexate treatment + laparoscopy

pregnancies in that group. The total number of nulliparous women was 42 (51.22%), slightly higher than women who had 1-2 births (47.56%). Of the total number of pregnancies, 71 (86.59%) were conceived spontaneously, while the ART procedure obtained 11 pregnancies (13.41%). In the surgically treated group, most women were 30-39 (58.62%) years of age, 24% were 20-29, and 17.24% were 40 and above. Considering the number of births in the aforementioned group, nulliparous patients (53.44%) and patients with 1-2 births (46.55%) occupy roughly the same percentage. There were more spontaneous pregnancies — 49 (84.48%) — than pregnancies resulting from the ART procedure (15.51%). Of the 15 patients treated with a

single dose of methotrexate, 46.66% were 30-39 years of age. Eight patients were nulliparous (53.33%) and 6 (40%) had 1-2 births all resulting from spontaneously conceived pregnancies. In the remaining two groups (expectant approach and methotrexate + surgery), the percentages are approximately the same as in the other groups.

Table 2 shows serum hCG levels among the four treatment groups. They were divided into six categories (< 1000 IU/L, 1000-2000 IU/L, 2000-3000 IU/L, 3000-4000 IU/L, 4000-5000 IU/L and > 5000 IU/L). All patients treated with a single dose of methotrexate had a serum hCG level below 2000 IU/L; 86.6% (13 patients) had a serum hCG level below 1000 IU/L

Table 2. *betaHCG level (IU/L)*

	LPSC	MTX	Expectant approach	MTX/LPSC
<1000	12 (20.69%)	13 (86.66%)	-	3
1000-2000	10 (17.24%)	2 (13.33%)	-	-
2000-3000	10 (17.24%)	0	-	-
3000-4000	7 (12.06%)	0	-	-
4000-5000	5 (8.62%)	0	-	-
>5000	14 (24.13%)	0	-	-

and 13.33% (2 patients) a serum hCG level below 2000 IU/L. In the group with surgically treated patients, serum hCG levels varied. The largest proportion of patients had a serum hCG level of > 5000 IU/L (24.13%, 14 patients), while 20.69% (12 patients) had a level below 1000 IU/L. The same number of patients had serum hCG levels of 1000-2000 IU/L and 2000-3000 IU/L. Other patients belong to the groups in between. All patients unsuccessfully treated with methotrexate had serum hCG levels of < 1000 IU/L. In patients treated with the expectant approach, a satisfactory drop in serum hCG levels was monitored until it became negative, so these values are not listed in the tables.

Discussion

We treated 15 patients (18.29%) with a single dose of methotrexate. Serum hCG in all these patients was below 2000 IU/L. In twelve of those patients (80%) methotrexate treatment was successful. The treatment was unsuccessful in three patients (20%), and subsequent laparoscopy was required. Therefore, a statistically significantly higher number of patients received the standard dose of methotrexate compared to those who later underwent the first surgical procedure ($P=0.0047$). Follow-up after methotrexate therapy took place on an outpatient basis. Serum hCG levels were determined on days 4 and 7, and compared with the initial level when methotrexate was administered (day 1)^{13,16}. The reasons for methotrexate treatment failure in our patients differed. In the first patient, a regular decline in serum hCG was observed, but on the 16th day of therapy the patient presented with severe pain in the lower abdomen and an ultrasound finding

of an adnexal mass. Another patient developed clinical symptoms of nausea, vomiting and abdominal pain one day after methotrexate administration. In addition to the above, an ultrasound examination showed a 14 mm free fluid in the pouch of Douglas and an echo of a coagulum near the ovary. The third patient received a two-dose regimen of methotrexate¹³. Despite such a dosage, an irregular rise in serum hCG level was observed with a suspicious ultrasound finding. All three patients underwent laparoscopic salpingectomy.

Research by Bonin *et al.* from 2017¹⁸ included 400 patients who received a single dose of methotrexate. The success rate of methotrexate therapy in this study was 78.5%. The need for laparoscopy indicated unsuccessful treatment. They confirmed a favorable factor for the success of methotrexate therapy is a serum hCG level of < 1000 IU/L, and that the success of methotrexate treatment decreases as the level of serum hCG increases. A systematic review by Menon *et al.* from 2006¹⁹ also confirmed that the failure of methotrexate therapy increases as serum hCG levels rise. A significant decrease in treatment success was observed in patients with serum hCG levels above 5000 IU/L, compared to patients whose initial dose was below 5000 IU/L. Lipscomb's work from 2007¹² also concluded that the serum hCG level is the best predictor of drug therapy success. Therapy success exceeded 90% when serum hCG levels were below 5000 IU/L, slightly dropping to 80% when levels were 5000-10000 IU/L. The success rate fell below 70% when levels exceeded 15000 IU/L. It was concluded that, in 88-92% of cases, a successful outcome of therapy can be expected. A Turkish trial from 2018²⁰, which included 101 patients who received one dose of methotrexate, reported a final success rate of 77.2%. Serum hCG levels below 1362 IU/L were considered

a reasonable threshold for determining treatment success. NICE guidelines¹⁵ recommend that patients with a serum hCG level below 1500 IU/L receive single-dose methotrexate therapy as first-line treatment. Patients with serum hCG levels 1500–5000 IU/L can be offered a decision between methotrexate therapy and surgery if the clinical presentation, ultrasound findings and the patient's cooperation allow it. The Royal College of Obstetricians and Gynaecologists states that a serum hCG level below 1500 IU/L is ideal, but treatment with methotrexate is possible for levels up to 5000 IU/L¹⁶. Finally, a different study by Jurkovic *et al.*, published in 2017¹⁴, compared the effectiveness of methotrexate therapy and a placebo to revise the conservative treatment of ectopic pregnancy. The success rate was 89% and 74% for methotrexate therapy and the placebo, respectively. Therefore, the study does not support routine use of methotrexate in clinically stable patients with a low serum hCG level, i.e. below 1500 IU/L. As for the group of patients with a serum hCG level above 1500 IU/L, further research is needed before they can be offered methotrexate as a safe and cost-effective alternative to surgery; this was also concluded in a study performed by Duz in 2022²¹.

Conclusion

To conclude, our success rate in the treatment of tubal ectopic pregnancy with a single dose of methotrexate was approximately equal to world trends. The serum hCG level remains a very important, but not exclusive, criterion for the decision on treatment. Serum hCG levels of 2000–5000 IU/L fall into a “grey area”. In such cases, the decision rests with the clinician and the treatment modality must be decided on a case-to-case basis according to the serum hCG level, clinical presentation, ultrasound findings and the patient's cooperation.

References

- Ivkošić IE, Bauman R, Ujević B, Vasilj O, Kojić IP, Ivkošić A, *et al.* Spontaneous heterotopic, ectopic cervical and ectopic tubal pregnancy—ever present diagnostic difficulty: three case reports. *Acta Clin Croat.* 2015 Sep;54(3):367–70.
- Šimunić V. *Gynecology.* Zagreb: Naklada Ljevak; 2001.
- Mann LM, Kreisel K, Llata E, Hong J, Torrone EA. Trends in ectopic pregnancy diagnoses in United States emergency departments, 2006–2013. *Matern Child Health J.* 2020;24(2):213–21. doi:10.1007/s10995-019-02842-0.
- Creanga AA, Shapiro-Mendoza CK, Bish CL, Zane S, Berg CJ, Callaghan WM. Trends in ectopic pregnancy mortality in the United States: 1980–2007. *Obstet Gynecol.* 2011;117(4):837–43. doi:10.1097/AOG.0b013e3182113c10.
- Lewis G. The Confidential Enquiry into Maternal and Child Health (CEMACH). Saving mothers' lives: reviewing maternal deaths to make motherhood safer—2003–2005. The Seventh Report on Confidential Enquiries into Maternal Deaths in the United Kingdom. London: CEMACH; 2007. p. 92–3.
- Ankum WM, Mol BW, van der Veen F, Bossuyt PM. Risk factors for ectopic pregnancy: a meta-analysis. *Fertil Steril.* 1996;65(6):1093–9.
- Mol BW, Ankum WM, Bossuyt PM, van der Veen F. Contraception and the risk of ectopic pregnancy: a meta-analysis. *Contraception.* 1995;52(6):337–41.
- Jacob L, Kalder M, Kostev K. Risk factors for ectopic pregnancy in Germany: a retrospective study of 100,197 patients. *Ger Med Sci.* 2017;15:Doc19.
- Refaat B, Dalton E, Ledger WL. Ectopic pregnancy secondary to in vitro fertilization embryo transfer: pathogenic mechanisms and management strategies. *Reprod Biol Endocrinol.* 2015;13:30.
- Brady PC. New evidence to guide ectopic pregnancy diagnosis and management. *Obstet Gynecol Surv.* 2017;72(10):618–25. doi:10.1097/OGX.0000000000000492.
- Condous G, Okaro E, Khalid A, Lu C, Van Huffel S, Timmerman D, *et al.* A prospective evaluation of a single-visit strategy to manage pregnancies of unknown location. *Hum Reprod.* 2005;20(5):1398–403. doi:10.1093/humrep/deh746.
- Lipscomb GH. Medical therapy for ectopic pregnancy. *Semin Reprod Med.* 2007 Mar;25(2):93–8.
- Tulandi T. Ectopic pregnancy: methotrexate therapy [Internet]. In: Schreiber CA, Chakrabarti A, editors. UpToDate. [cited 2024 Aug 15]. Available from: <https://www.uptodate.com/contents/ectopic-pregnancy-methotrexate-therapy>.
- Jurkovic D, Memtsa M, Sawyer E, Donaldson AN, Jamil A, Schramm K, *et al.* Single-dose systemic methotrexate vs expectant management for treatment of tubal ectopic pregnancy: a placebo-controlled randomized trial. *Ultrasound Obstet Gynecol.* 2017 Feb;49(2):171–6.
- Ectopic pregnancy and miscarriage: diagnosis and initial management [Internet]. London: National Institute for

- Health and Care Excellence (NICE); 2019 Apr [updated 2023 Aug 23; cited 2024 Aug 20]. Available from: <https://www.nice.org.uk/guidance/ng126>.
16. Diagnosis and management of ectopic pregnancy: Green-top Guideline No. 21 [Internet]. London: Royal College of Obstetricians and Gynaecologists (RCOG); 2016 Dec [updated 2022 Jun; cited 2024 Aug 1]. Available from: <https://www.rcog.org.uk>.
 17. Taran FA, Kagan KO, Hübner M, Hoopmann M, Wallwiener D, Brucker S. The diagnosis and treatment of ectopic pregnancy. *Dtsch Arztebl Int*. 2015 Oct 9;112(41):693-703.
 18. Bonin L, Pedreiro C, Moret S, Chene G, Gaucherand P, Lamblin G. Predictive factors for methotrexate treatment outcome in ectopic pregnancy: a comparative study of 400 cases. *Eur J Obstet Gynecol Reprod Biol*. 2017 Jan;208:23-30.
 19. Menon S, Collins J, Barnhart KT. Establishing a human chorionic gonadotropin cutoff to guide methotrexate treatment of ectopic pregnancy: a systematic review. *Fertil Steril*. 2007 Mar;87(3):481-4.
 20. Pulatoglu C, Dogan O, Basbug A, Kaya AE, Yildiz A, Temizkan O. Predictive factors of methotrexate treatment success in ectopic pregnancy: a single-center tertiary study. *North Clin Istanbul*. 2018 Sep;5(3):227-31.
 21. Düz SA. Fertility outcomes after medical and surgical management of tubal ectopic pregnancy. *Acta Clin Croat*. 2022 Feb;60(3):347-53. doi:10.20471/acc.2021.60.03.02.

Sažetak

PRIMJENA METOTREKSATA U TERAPIJI TUBARNE IZVANMATERNIČNE TRUDNOĆE

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Svrha je ovog rada prikazati rezultate našeg istraživanja i usporediti ih s ostalim recentnim radovima koji se bave ovom temom.

Metode: U Klinici za ginekologiju i porodništvo Kliničkog bolničkog centra Sestre milosrdnice u periodu od godine dana (studen 2022. do studen 2023.) hospitalizirane su i liječene ukupno 82 pacijentice s ektopičnom tubarnom trudnoćom. Podaci pacijentica uspoređivani su prema metodi liječenja, incijalnoj razini humanog korionskog gonadotropina (hCG) iz krvi te osnovnim demografsko-maternalnim parametrima (godiste, paritet, način zanošenja).

Rezultati: Najveći broj naših pacijentica, njih 58 (70,73 %), liječen je operativno laparoskopskom salpingektomijom, 15 (18,29 %) pacijentica liječeno je standardnom dozom metotreksata, a kod tri pacijentice (3,65 %) koje su primile metotreksat liječenje nije bilo uspješno te je bio potreban operativni zahvat. Razina hCG-a iz krvi kod svih pacijentica liječenih metotreksatom bila je ispod 2000 IU/L. Većina pacijentica spadala je u dobnu skupinu 30-39 godina, više od pola bile su nerotkinje, a 71 trudnoća bila je spontano začeta.

Zaključak: Naša uspješnost liječenja metotreksatom otprilike prati svjetske trendove. Razina hCG-a u krvi je važan, ali ne i isključivi kriterij za odluku o liječenju. Potrebna su daljnja istraživanja o načinu liječenja pacijentica s razinom hCG-a između 2000 i 5000 IU/L mirne kliničke slike i neupadljivog ultrazvučnog nalaza.

Ključne riječi: *Ektopična trudnoća; Metotreksat; hCG; Ekspektativni pristup*