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METHOTREXATE THERAPY IN GYNECOLOGIC PATIENTS: FOUR-YEAR EXPERIENCE AT A TERTIARY REFERRAL CENTER

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Aim: The aim of this study was to present methotrexate treatment results in ectopic pregnancy and gestational trophoblastic neoplasia (GTN) at a tertiary referral center. ***Methods***: A retrospective case-series study was conducted using data from records of patients treated with methotrexate during a 4-year period at Merkur University Hospital in Zagreb, Croatia. The study included 11 patients divided into 2 groups: 6 patients with ectopic pregnancy (5 tubal and 1 cornual) and 5 patients with low-risk GTN. Patients with ectopic pregnancy were treated with single dose methotrexate protocol (1 mg/kg/day intramuscularly), whereas those with low-risk GTN were treated with 8-day single-agent methotrexate along with leucovorin rescue protocol. ***Results:*** Among 5 tubal pregnancies, methotrexate treatment was successful in 4 (80%) cases, while one patient required surgical treatment. One case of cornual pregnancy also required surgical treatment after ineffective methotrexate treatment. Of 5 GTN cases treated with methotrexate, 3 required further EMA-CO treatment and 1 required additional surgical treatment, yielding the overall success rate of methotrexate treatment of 20%. ***Conclusion:*** Methotrexate is a valuable medication for treatment of appropriately selected ectopic pregnancy cases, while its usefulness and efficiency in the treatment of low-risk GTN diseases has not been confirmed.

Key words: methotrexate, ectopic pregnancy, gestational trophoblastic disease, gestational trophoblastic neoplasia, invasive mole, choriocarcinoma

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INTRODUCTION

Methotrexate (MTX) is a folic acid antagonist that inhibits cell division by interfering with DNA synthesis and cell replication (1). It has been used for more than 50 years as a chemotherapy agent and immune system suppressant in the treatment of various medical conditions, primarily tumors and autoimmune diseases. In gynecology, MTX has found its use in the treatment of two disorders, ectopic pregnancy and gestational trophoblastic neoplasia (GTN).

An ectopic pregnancy mostly occurring in the fallopian tube can also be cervical, ovarian, abdominal, interstitial (cornual) or located in a previous cesarean section scar. The incidence of ectopic pregnancy is increasing worldwide (mainly due to the increased incidence of pelvic inflammatory disease and assisted reproduction technologies) and is reported to be between 0.5% and 2% (11.5 *per* 1000 pregnancies) (2, 3). Optimal candidates for MTX treatment of ectopic pregnancy are hemodynamically stable patients, willing and able to comply with post-treatment follow-up, having a human chorionic gonadotropin (hCG) serum value ≤5000 mIU/mL and no fetal cardiac activity in ectopic gestational sac (4). The size of ectopic mass being less than 3 to 4 cm is also commonly used as a patient selection criterion; however, this has not been entirely confirmed as a predictor of successful treatment. Two most commonly used protocols for MTX administration are single and multiple dose ones (four MTX doses which alternate with leucovorin). In 15% of cases, surgery is required due to treatment failure (3).

Gestational trophoblastic neoplasia (GTN) is a term used for malignant forms of gestational trophoblastic disease and includes the following conditions: invasive mole, choriocarcinoma, placental site trophoblastic tu-

mor and epithelioid trophoblastic tumor. These tumors develop following some form of pregnancy, half of them after hydatidiform mole, one-forth develop after miscarriage or tubal pregnancy and the remaining fourth develop after normal pregnancy and are usually diagnosed by persistently elevated serum human chorionic gonadotropin (hCG) levels (5). The first report of MTX therapy of GTN appeared in 1956 (6) and today it has become the first choice of treatment for low-risk GTN. GTN is staged clinically and classified into low-risk or high-risk disease according to the FIGO/WHO scoring system (7). Patients with high-risk disease are primarily treated with combination chemotherapy, EMA-CO (etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine), since single-agent chemotherapy has shown low efficiency. On the other hand, MTX is the first choice therapy for low-risk disease, which includes non-metastatic neoplasia (except for lung metastasis), where the WHO score is 6 or less in FIGO stage I-III. The aim of this study was to present MTX treatment cases and compare treatment results at our center.

PATIENTS AND METHODS

A retrospective case-series study was conducted using data from medical records of patients treated with MTX from October 2012 until May 2017 at the Department of Gynecology and Obstetrics, Merkur University Hospital, a tertiary referral center in Zagreb, Croatia. Patients treated with MTX were identified in medical records. During this 4 and a half-year period, 11 women were treated with MTX, among which 6 women were treated for ectopic pregnancy and 5 for low-risk GTN disease. Of the 6 cases of ectopic pregnancy, 5 tubal and 1 case of cornual pregnancy were diagnosed. General data (age, gravidity, parity) were collected with special attention to data relevant for determined study outcomes, i.e. hCG levels, indication for MTX treatment, as well as treatment response and outcome for both ectopic pregnancy and GTN. Single dose protocol was used in all cases treated for ectopic pregnancy (1 mg/kg MTX intramuscularly (im)) and hCG values were checked on days 4-5 and days 7-9. Second dose was administered if decrease in hCG levels between these two days was less than 15 percent. After second testing, hCG testing was repeated weekly until it became negative. Patients included in this study with the diagnosis of GTN were those with low-risk disease according to the FIGO/WHO scoring system and were treated with the 8-day single-agent MTX along with leucovorin (folic acid) rescue protocol. The dosage was 50 mg/day im on days 1, 3, 5 and 7 with leucovorin 15 mg im 24 hours after each dose of MTX on days 2, 4, 6 and 8. From that time, hCG levels were measured weekly and, in case of persistently elevated hCG levels, an additional 8-day single agent MTX protocol was repeated. If after two cycles no symptom improvement was observed and/or hCG values were rising, further management was discussed with patients and either another course of single agent treatment or treatment with EMA/CO protocol (etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine) was applied. The study had received approval of the departmental clinical board. Since personal data of patients were not used, the patient informed consent was not required.

RESULTS

During the study period, 11 women were treated with MTX. Data on 6 patients with ectopic pregnancy, i.e. age, gravidity, parity, hCG levels before and after MTX administration, as well as treatment outcomes are shown in Table 1. Among 5 tubal pregnancies, single dose MTX protocol was successful in 4 (80%) cases, with 1 case treated surgically due to failure of MTX therapy (patient No. 5). In this case, after initial treatment with single dose MTX, hCG levels rose on day 4 without expected decline of hCG levels on day 7. The patient was reluctant to receive a repeated course of MTX. hCG values continued to rise on day 10, and ultrasound examination on day 11 revealed free fluid in Douglas cavity suggestive of abdominal bleeding. A decision was made to perform laparoscopic unilateral salpingectomy. The diagnosis of ectopic pregnancy was confirmed by histopathology. The study included 1 case of cornual pregnancy treated by MTX (patient No. 6). The diagnosis was made on ultrasound examination showing a gestational sac separate from the uterine cavity and myometrial thickness of less than 5 mm, along with a hCG value of 953 IU/L. Seven days after administration of the first single dose of MTX, the patient developed abdominal pain and signs suggestive of abdominal bleeding. Rupture of cornual pregnancy was found during surgery.

Table 1.
Data and treatment outcomes in patients with ectopic pregnancy: age, gravidity, parity, and hCG levels

No	Age (yrs)	GxPx	hCG before MTX	hCG MTX day 4/5	hCG MTX day 7/9	hCG MTX week 2	hCG MTX week 3	hCG MTX week 4
1	43	G2P1	757	/	920	441	184	37
2	29	G4P1	263	/	/	36	/	/
3	26	G2P0	252	245	/	122	31	/
4	37	G2P0	519	749	563	220	30	8
5	40	G2P0	1031	1873	1638	LPSC		
6*	27	G2P1	953	LAP				

hCG = human chorionic gonadotropin (IU/L); G = gravidity; P = parity; LPSC = laparoscopy; LAP= laparotomy; 6* = case of cornual pregnancy

Table 2.
Data and treatment outcomes in patients with gestational trophoblastic neoplasia: age, gravidity, parity, and hCG levels

No.	Age (yrs)	GxPx	hCG initial*	hCG max* after D&C	hCG before MTX*	hCG MTX wk 1**	hCG MTX wk 2	hCG MTX wk 3	hCG MTX wk 4	Outcome
7	17	G1P0	>225000	115981	107112	76262	36853	3921	754	Recovery without any further interventions
8	46	G3P1	>709000	36738	36738	31113	5852	6872	9400	EMA-CO after 2 courses of MTX treatment
9	49	G11P5	>373000	50771	6030	1306	390	292	316	Abdominal hysterectomy and bilateral adnexectomy, negativization of hCG
10	49	G7P3	>74000	7203	7203	/	/	4110	5869	EMA-CO after 2 courses of MTX treatment and surgery (abdominal hysterectomy and bilateral adnexectomy)
11	25	G2P1	>94000	5420	5420	/	4521	/	1988	Further chemotherapy with EMA-CO required

G = gravidity; P = parity; D&C = dilatation and curettage; hCG = human chorionic gonadotropin; *hCG initial represents the first hCG value upon which gestational trophoblastic disease (neoplasia) was suspected, hCG max after D&C refers to the maximal hCG value measured during the period between the first dilatation and curettage performed and administration of MTX therapy, while hCG before MTX represents the final value before administration of MTX therapy: **hCG MTX + week refers to the period of hCG measurement after MTX treatment

In total 5 cases of GTN were treated with MTX. Among them, 3 developed from partial hydatidiform mole (patients Nos. 7, 10 and 11), while the remaining 2 developed from complete hydatidiform mole (patients Nos. 8 and 9). All 5 cases were low-risk diseases according to the FIGO/WHO scoring system. Data on patients with GTN, i.e. age, gravidity, parity, hCG levels (initial, after dilatation and curettage, and then weekly), as well as treatment outcomes are shown in Table 2. Patients Nos. 7, 8, 10 and 11 had invasive mole. Patient No. 7 recovered after the first course of single agent multiple MTX treatment and was alive and well during the follow-up. Patient No. 11 had no follow-up after the first week of single agent multiple MTX treatment. The patient attended follow-up after 4 weeks without satisfactory decrease of hCG values and was offered further treatment with EMA/CO protocol. Similarly, patients Nos. 8 and 10 had good initial response but after 4 weeks and a repeated course of single agent multiple MTX treatment had a rise of hCG values and were also treated by EMA-CO protocol. All these 3 patients (Nos. 8, 10 and 11) attended follow-up at 4-6 months after completed treatment and were alive and well with negative values of hCG. Patient No. 9 had choriocarcinoma. There were no signs of metastases and she was also listed as low-risk. However, after initial treatment with good response and decline of hCG values, continuously elevated hCG values despite repeated single agent multiple MTX treatment were observed. Considering this, in combination with persistent vaginal bleeding, age of 49 years, ovarian theca lutein cysts and pelvic pressure, a decision was made to perform hysterectomy and bilateral salpingoophorectomy on the patient's request. The patient recovered well and hCG values were slightly elevated after one and two weeks following surgery but became negative a week later and remained negative during follow-up.

DISCUSSION

During the study period, there were 99 cases of ectopic pregnancy at our department and only 6 of them were treated by MTX, yielding an incidence of 6% of ectopic pregnancies treated by MTX. The success rate for treatment of tubal ectopic pregnancies with MTX was 80%, while the single case of cornual pregnancy was not successfully treated with MTX. According to the available literature, the success rate of MTX treatment ranges between 63% and 97%. Such a difference is due to the heterogeneity of patient groups, different inclusion criteria used and differences in MTX treatment protocols. In a randomized trial by Song *et al*., the success rate of the single-dose protocol was 83% (8). Lipscomb *et al*. report an even higher success rate of 90.7% (9), whereas a tertiary center from Turkey reports a success rate of 93.0% (10). The single best prognostic indicator of successful MTX treatment is initial serum hCG level (11). In a study by Menon *et al*., the reported failure rates were 1.5% if initial hCG level was <1000 mIU/mL and 5.6% if initial hCG levels were between 1000 and 2000 mIU/mL (12). This is in concordance with our results where all cases with initial hCG level below 1000 IU/L responded well to treatment. Only one case had initial hCG level above 1000 IU/L and was ultimately treated surgically. In our case series, the single dose protocol was applied in all cases (1 mg/kg/day im). Another treatment option is 50 mg of MTX *per* square meter of body surface area (BSA). The hCG concentration usually declines to less than 15 mIU/mL by day 35 post injection (13). If the hCG does not decline to zero, a new pregnancy should be excluded; if hCG is rising, transvaginal ultrasound should be performed in order to exclude persistent disease with possible complications. In case No. 5, ultrasound examination was performed after an

increase in hCG level had been observed, and revealed a persistent ectopic gestational sac with free fluid in Douglas cavity. Surgical treatment was performed. Our study included 1 case of cornual pregnancy treated with MTX. According to RCOG Green-top Guidelines, excision of rudimentary horn where cornual pregnancy is present seems to be the best approach in the treatment of cornual pregnancy (4). However, a recently published case study describes successful treatment of cornual pregnancy with multi-dose protocol of MTX and folic acid (14). In our case, we attempted medical treatment of cornual ectopic pregnancy since hCG values were low and the patient had no clinical symptoms. Unfortunately, hCG values were not checked on day 4, and on day 7 prior to hCG testing the patient had rupture of cornual ectopic pregnancy.

Low-risk GTN is another indication for MTX treatment. Treatment protocols vary among medical centers worldwide and several drug schedules exist. Three most often used options are as follows: MTX 0.4 mg/kg intramuscularly (im) for 5 days, repeated every 2 weeks. This protocol has a primary failure rate of 11%-15% for non metastatic disease and 27%-33% for metastatic disease (15); MTX 50 mg im or 1 mg/kg every other day for 4 doses with leucovorin 15 mg or 0.1 mg/kg 24-30 hours after each dose of MTX is a widely used protocol but has a 20%-25% primary failure rate (16); and MTX 50 mg/m^2 BSA im given weekly is the least successful regimen with a 30% primary failure rate (17). There were 5 cases of GTN during the study period, all of them being confirmed by histopathology. All patients included in our study had low-risk GTN disease and were treated with the 8-day single-agent MTX with folic acid leucovorin rescue protocol. The overall success rate of the initial MTX treatment was only 20%, however, the numbers are small. Three of 5 (60%) cases required further multiple agent chemotherapy by EMA-CO (etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine). In one case, despite multiple MTX treatments, the patient still had signs of trophoblastic activity. Considering her age, symptoms and request for definitive treatment, hysterectomy was performed. The EMA-CO protocol is a highly effective second line treatment for high-risk GTN. In a study by Turan *et al.*, 33 patients with high-risk GTN were treated, 23 of them primarily with EMA-CO and 10 secondarily with EMA-CO after failure of single agent or MAC (methotrexate, actinomycin D, cyclophosphamide, or clorambucile) treatment. Survival rate was 91.3% (21/23) for primary treatment and 90% (9/10) for secondary treatment (18). In our case series, 3 patients received EMA-CO protocol and on follow-up all were alive and well. Success rate in our case series was lower than in previously published studies, where the overall success rate of treatment of low-risk GTN disease with MTX was 74% in a study performed in Turkey (19) and 83% in a study from Saudi Arabia (20). In a study conducted by Sita-Lumsden *et al.*, the success rate of single-dose MTX treatment ranged from 75% for FIGO score 0-1 through to 31% for those with FIGO score 6 (21). The low success rate in our study may have been due to erroneous classification of GTN disease, however, to the best of our knowledge, all patients met the criteria for low-risk group and therefore had an indication for treatment with the single agent MTX 8-day protocol. The diagnosis was based on high trophoblastic activity after evacuation of the uterus for hydatidiform mole and signs of invasive trophoblastic activity on ultrasound and color Doppler examination, which has been proven as a useful supplementary tool in the diagnosis and management of GTN (22, 23). Choriocarcinoma is more likely to develop after complete hydatidiform mole and it was the case in patient No 9.

Limitations of this study include small sample size consisting of only 6 cases of ectopic pregnancies and 5 cases of low-risk GTN disease eligible for MTX treatment. Furthermore, even though all low-risk GTN cases were managed and treated according to the same protocol, a single unified protocol for this condition does not exist at our department, which is essential when dealing with such serious and distinctive medical conditions. Also, some cases lacked appropriate follow-up (patients Nos. 6 and 10), which might have had an impact on further management of these patients. All of this will be addressed in future management of gestational trophoblastic disease and hopefully yield improved success rates of treatment with MTX, especially concerning GTN.

CONCLUSION

The results of this study confirmed the usefulness of MTX in the treatment of ectopic pregnancies, particularly when eligible cases are attentively and appropriately selected according to available medical information. A success rate of 80% for the treatment of tubal ectopic pregnancies proves MTX to be a potent drug for the treatment of this condition. Efforts should be made to raise awareness among women affected with these conditions and among medical practitioners involved in their treatment regarding the usefulness and advantages of MTX treatment of ectopic pregnancies. The usefulness of MTX treatment for low-risk GTN disease was not confirmed in this study. With a success rate of only 20% (other cases requiring further combination chemotherapy or surgery), we were unable to confirm at our department the efficiency of MTX treatment of low-risk GTN disease as suggested by the FIGO Committee on Gynecologic Oncology (24). Ad-

ditional research, as well as follow-up of a larger number of our patients is needed to investigate the reasons of this low success rate.

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SAŽETAK

TERAPIJA METOTREKSATOM GINEKOLOŠKIH PACIJENTICA: ČETVEROGODIŠNJE ISKUSTVO U TERCIJARNOJ ZDRAVSTVENOJ USTANOVI

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Cilj: Cilj rada je prikazati rezultate liječenja metotreksatom dviju ginekoloških bolesti u tercijarnom referentnom centru. ***Metode:*** Provedena je retrospektivna studija uporabom podataka iz povijesti bolesti pacijentica liječenih metotreksatom tijekom četverogodišnjeg razdoblja u Kliničkoj bolnici Merkur, Zagreb, Hrvatska. U studiju je uključeno 11 pacijentica koje su podijeljene u 2 skupine: 6 pacijentica s ektopičnom trudnoćom (5 tubarnih i 1 kornualna) i 5 pacijentica s gestacijskom trofoblastičnom neoplazijom (GTN) niskog rizika. Pacijentice s ektopičnom trudnoćom liječene su jednokratnom dozom metotreksata (1 mg/kg/dan intramuskularno), dok su pacijentice s GTN niskog rizika liječene osmodnevnim protokolom metotreksatom i leukovorinom. ***Rezultati:*** Od 5 pacijentica s tubarnom trudnoćom liječenje metotreksatom bilo je uspješno u 4 (80%) slučaja, dok je u 1 slučaju bilo potrebno kirurško liječenje. U 1 zabilježenom slučaju kornualne trudnoće liječenje metotreksatom bilo je neuspješno te je pacijentica zbrinuta kirurški. Od 5 slučajeva GTN liječenih metotreksatom u 3 slučaja bio je potreban nastavak kemoterapije po EMA-CO protokolu, dok je u 1 slučaju bilo potrebno dodatno kirurško liječenje te je ukupna uspješnost liječenja metotreksatom iznosila 20 %. ***Zaključak:*** Metotreksat se može smatrati učinkovitom terapijom u liječenju pažljivo odabranih pacijentica s ektopičnom trudnoćom, dok njegova uspješnost u kemoterapijskom liječenju GTN niskog rizika nije potvrđena.

Ključne riječi: metotreksat, ektopična trudnoća, gestacijska trofoblastična bolest, gestacijska trofoblastična neoplazija, invazivna mola, koriokarcinom