High live birth rate after conservative treatment of ectopic pregnancy with Methotrexate

Wysoka częstość żywych urodzeń po zachowawczym leczeniu ciąż ektopowych Metotreksatem

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Abstract

Objectives: *The aim of the study was to assess fertility in patients diagnosed with ectopic pregnancy and treated with methotrexate, as well as safety and efficacy of conservative treatment. Also, risk factors of recurrent ectopic pregnancies were determined.*

Material and methods: *The study included 86 female patients with ectopic pregnancy, hospitalized and treated in the clinic of Gynecological Endocrinology, UJCM, Cracow, between 2007 and 2011. A total of 73 patients received a single dose of MTX in the amount of 50mg/m2 of body surface area. Serum b-hCG concentration was measured on days 4 and 7. The treatment was considered successful when b-hCG concentrations dropped to less than 0.2mIU/ml without surgery.*

Results: *Among 34 patients on follow-up, 8 (23.5%) did not attempt to conceive again, whereas 26 patients declared their wish to conceive again. The attempt proved to be successful in case of 16 women (61.53%), and they gave birth to healthy children. Average time to pregnancy was 14.9 months (SD±10.9). The first pregnancy occurred after 6 months and the last after 35 months. No congenital birth defects were found in the newborns.*

Conclusions: *Systemic, conservative treatment with methotrexate is an effective and safe way of managing ectopic pregnancy, even in cases with higher b-hCG concentrations. Most patients can be successfully treated without surgery, thus they may even be treated in outpatient settings. High fertility can be maintained and is independent of the skills of the operators and access to laparoscopic techniques. Conservative treatment does not increase the risk of recurrent ectopic pregnancy but should be offered in wards that provide 24-hour surgical care.*

Key words: **ectopic pregnancy** / **methotrexate** / **fertility** / **conservative treatment** /

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Streszczenie

Cel pracy: *Badanie miało na celu ocenę płodności pacjentek ze zdiagnozowaną ciążą pozamaciczną leczonych metotreksatem, skuteczność i bezpieczeństwo leczenia zachowawczego oraz poszukiwanie czynników ryzyka powtórnej ciąży pozamacicznej.*

Materiał i metody: *86 pacjentek ze zdiagnozowaną ciążą pozamaciczną było objętych leczeniem w Klinice Endokrynologii Ginekologicznej UJCM w Krakowie od 2007 do 2011 roku. Po zakwalifikowaniu u 73 pacjentek zastosowano terapię pojedynczej dawki metotreksatu w ilości 50 mg/m^2 powierzchni ciała. Kolejno oceniano stężenia b-hCG w surowicy krwi w dniu czwartym i siódmym terapii. Za sukces terapeutyczny uznawano obniżenie wartości b-hCG poniżej 0,2 mIU/ml bez konieczności wykonania zabiegu operacyjnego.*

Wyniki: *Pośród 34 pacjentek z przebywających w opiece przyklinicznej, 8 (23,5%) nie zdecydowało się na kolejną ciążę. 26 pacjentek zdeklarowało plany reprodukcyjne, 16 (61,53%) z nich urodziło zdrowe dzieci. Średni czas do uzyskania ciąży wynosił 14,9 (SD 10,9) miesiąca. Pierwsza ciąża wystąpiła po 6 miesiącach a ostatnia obserwowana po 35 miesiącach. Nie zaobserwowano żadnych wad wrodzonych u urodzonych dzieci.*

Wnioski: *Systemowe leczenie zachowawcze metotreksatem jest terapią skuteczną i bezpieczną nawet przy wyższych wartościach b-hCG niż 3500 mIU/ml. Umożliwia wyleczenie większości pacjentek bez konieczności wykonywania zabiegu operacyjnego, nawet w trybie ambulatoryjnym. Pozwala na utrzymanie wysokiej płodności niezależnie od umiejętności operatora i dostępności technik laparoskopowych. Leczenie zachowawcze nie zwiększa ryzyka rozwoju ponownie ciąży pozamacicznej.*

Słowa kluczowe: **ciąża ektopowa** / **metotreksat** / **płodność** / **leczenie zachowawcze** /

Introduction

The frequency of ectopic pregnancies has been on the rise. *The Center for Disease Control and Prevention* (CDC) estimated that in 1992, 1.97% of all pregnancies were ectopic. Currently, CDC reports the percentage to have risen to 2.07-2.43% [1]. Furthermore, they report a 6-fold increase in ectopic pregnancies (from 17 800 cases in 1970 to 108 000 cases in 1992), related to widespread access to assisted reproductive technologies (ART) [2], greater prevalence of sexually transmitted diseases, and increased incidence of pelvic inflammatory diseases (PID) [2, 3] – especially due to C*hlamydia trachomatis* infections [4, 5, 6, 7].

Until the end of the 1980s, laparoscopy has remained the main diagnostic tool for ectopic pregnancy. In the last decade, the development of ultrasonography has allowed improvements in the diagnosis with sufficient sensitivity and specificity of incorrectly implanted embryos. The sensitivity and specificity of a single transvaginal ultrasonography test (TVS) are 74% (95% CI:65.1 – 81.6) and 99.9% (95% CI:99.8 – 100), respectively [8]. It is estimated that 60% of ectopic pregnancies appear as a heterogeneous mass adjacent to the ovary – a '*blob sign'*, 20% as an area with a hyperechogenic ring – a '*bagel sign'*, and 13% as a gestational sac containing a fetal pole with present or absent heart activity. TVS is the gold standard in the early diagnosis of any type of ectopic pregnancy, whereas laparoscopy only has a role in case of treatment intervention [9]. There also exists a small group of women with a positive pregnancy test and an uncharacteristic image in TVS testing, described in the literature as PUL (Pregnancy of Unknown Location).

The second essential factor in diagnosing an ectopic pregnancy is the concentration of human chorionic gonadotropin (hCG) in the blood serum. In the 1960s, there was an improvement in the method used to determine the b-hCG subunit in urine as low as 1000 mIU/ml, which allowed for this method to be used in the early diagnosis of ectopic pregnancy [10].

Presently used immunoenzymatic (ELISA) methods can show b-hCG levels of 15 mIU/ml in the blood serum within one hour. Additionally, in a series of tests, a slower increase in b-hCG in the blood serum is observed in cases of ectopic pregnancies, compared to the physiological doubling within 48 hours in eutopic pregnancies. The risk for an ectopic pregnancy is high if the observed increase of the value is less than 66%. The use of the diagnostic method of increasing b-hCG levels alone results in 13% of ectopic pregnancies being undiagnosed. Moreover, a lower than expected rise in b-hCG levels may also be observed in 15% of normal pregnancies [11]. Presently, early diagnosis of ectopic pregnancy is based on combining the TVS evaluation with serum b-hCG concentration.

Since 1849, when the first operation due to intra-abdominal hemorrhage caused by an ectopic pregnancy was performed [12], laparoscopic techniques have started to replace laparotomy and become an essential part of the treatment. Simultaneously, in 1985, Chotiner was the first to report a successful treatment of a fallopian tube pregnancy using methotrexate (MTX) [13], beginning an era of conservative management. Methotrexate, a folic acid antagonist, disrupts proper DNA synthesis, thus inhibiting cell proliferation. Trophoblastic tissue is especially sensitive to the effect of this cytostatic drug. With regard to its mechanism of action, it is important to note strong anti-inflammatory properties [14] of MTX, which may have a positive influence on improving fertility in the future. Various schemes of conservative treatment are used. Due to high costs of hospitalization, a benefit was demonstrated in patients with conservative MTX treatment in a scheme of multiple doses, where b-hCG concentrations were <1500 mIU/ml [15]. In contrast to this scheme, application of a single dose in the amount of 50 mg/m2 of body surface area contributed to the reduction of treatment costs by shortening the duration of hospitalization, which also justifies the use of conservative treatment in higher b-hCG concentrations. Special

attention is given to the fact that the treatment may be used in outpatient practices [16]. MTX given locally, both under TVS as well as laparoscopic control [14], did not demonstrate significant differences as compared to intramuscular administration. The advantages of systemic administration include simplicity of therapy, independence of the skills of the operator, as well as the possibility of treatment in outpatient settings.

A negative effect on fertility due to MTX treatment has not been observed [17, 18, 19, 20]. More importantly, no negative effect on the ovarian reserve has been noted, either [21]. The most common etiology of ectopic pregnancy is considered to be the clinical or sub-clinical inflammation of the fallopian tubes, possibly leading to irreversible and bilateral damage of their function. Consequently, this results in recurrences of incorrectly implanted pregnancies or difficulties to conceive [22]. Conservative treatment with MTX, due to its strong anti-inflammatory properties, may positively influence the function of the opposite fallopian tube, thus contributing to improving further procreation.

The time period of complete excretion of MTX from the body is 4 – 6 months [23, 24]. The fact that MTX therapy is safe for future offspring is particularly noteworthy. In retrospective studies, no differences were demonstrated in the frequencies of fetal defects between patients who conceived within 3 months (3.6 SD=1.7) into the MTX treatment as compared to those who conceived after a longer period of time (23.6 SD=14.7) [25]. The risk was equal to that of the general population.

Objectives

The aims of the study were to evaluate fertility of patients diagnosed with an ectopic pregnancy and treated with MTX, to assess the safety and efficacy of conservative treatment, and to determine the risk factors of recurrent ectopic pregnancies.

Material and methods

A total of 86 female patients diagnosed with an ectopic pregnancy were hospitalized and treated in the clinic of Gynecological Endocrinology, UJCM, Cracow, between 2007 and 2011. The diagnosis was established on the basis of an abnormal increase in b-hCG concentrations and ultrasonographic (TVS) confirmation of changes in the paraovarian region with the aid of the GE Voluson 730 Expert, or on the basis of b-hCG > 1000 mIU/ml and absence of a gestational sac in the uterine cavity.

Among the 73 patients who were qualified for conservative MTX treatment, none of the pregnancies displayed signs of fetal cardiac activity or signs of active hemorrhage into the abdominal cavity. Excluding criteria were: hemodynamic instability, signs of peritonitis, heterotopic pregnancy, contraindications to administering methotrexate (e.g. leukopenia, thrombocytopenia, elevated liver enzymes, or biochemical indicators of renal insufficiency). After obtaining written consent for the proposed treatment plan, the patients received a single dose of MTX in the amount of 50mg/m2 of body surface area. Subsequently, serum b-hCG concentration was measured on days 4 and 7 after the first dose. Also, blood morphology and liver enzymes were monitored. If a decrease of at least 30% of the maximum b-hCG value was observed, the patient was discharged from the ward and instructed to monitor b-hCG concentrations weekly at the outpatient clinic and to undergo TVS testing until complete disappearance of b-hCG. After the completion of therapy, OCP was recommended for a period of 3 months and telephone contact with the primary care physician was ensured. Furthermore, folic acid supplementation in prophylactic dosage was added in patients who did as well as did not intend to conceive in the future.

The next dose of MTX was administered to those patients in whom b-hCG concentrations decreased by less than 15%, remained constant, or increased between days 4 and 7 after initiating the first dose. Subsequent doses were administered until a satisfactory decrease in serum b-hCG concentration was obtained or signs of adverse effects due to the medication appeared. The maximal dose of MTX was 200mg throughout the course of the treatment and the treatment regimen was in compliance with the guidelines for initiating and withdrawing the medication. Patients were instructed to attend regular follow-up visits at the outpatient clinic 12, 18, 24 and 36 months after treatment completion, especially in cases when they wished to conceive again.

The treatment was considered successful when b-hCG concentrations dropped to less than 0.2mIU/ml after initiating conservative therapy without the need of surgical intervention.

In cases of observation loss, i.e. the patient did not appear at the outpatient clinic 12, 18, 24 and 36 months after treatment completion, telephone contact was made in order to determine their procreative status.

Statistical analyses were conducted with STATISTICA 10. The Shapiro-Wilk test was used for the analysis of normally distribution variables. Means, median, standard deviations, as well as minimum and maximum values, were calculated for continuous data. The Mann-Whitney test was used for group comparisons of continuous variables. The chi-square test for independence was used for group comparisons of categorical variables. $p < 0.05$ was considered as statistically significant.

Results

A total of 86 patients participated in the study and after fulfilling the criteria for initiating and withdrawing MTX, 73 patients (84.9%) qualified for conservative treatment, 12 patients (14%) qualified for the surgical treatment and in 1 patient (1.1%) the treatment was observational. Despite conservative treatment, intra-abdominal hemorrhage occurred in 6 patients (7%) during hospitalization and surgical intervention was required. The fact that there was only one case of fallopian tube perforation during the surgical intervention is particularly noteworthy.

The average length of hospitalization in patients undergoing conservative treatment was 9.7 days (SD±5.2). The average concentration of b-hCG upon admission was 3569.8 mIU/ml (SD±4552.9), with a maximum b-hCG concentration of 4809.3 mIU/ml (SD ±6079.4). Upon discharge, the average concentration of b-hCG was 2234.7 mIU/ml (SD±3202.4), indicating a decrease of b-hCG by 57.5% (SD±25.1) in relation to the maximal values during hospitalization. In the majority of patients, intramuscular 150 mg MTX (48.8%) was injected in three doses, 50 mg each. The characteristics of the analyzed groups in terms of the length of hospitalization, age, BMI, obstetric history, b-hCG concentrations, as well as symptoms upon admission, are presented in Table I. The decrease of b-hCG to undetectable levels took approximately 45 days.

Table I.

Age (years)		30.0 ±4.8	
BMI (kg/m2)		22.6 ± 3.1	
Next pregnancy	First pregnancy	47	54%
	Next pregnancy	39	46%
Number of the current pregnancy	First	47	54%
	Second	22	25.58%
	Third	13	15.11%
	Fourth	1	1.16%
	Fifth	3	3.48%
Number of prev. D&C	0	75	87.2%
	1	9	10.46%
	2	1	1.16%
	4	1	1.16%
Number of prev. vaginal deliveries	0	71	82.55%
	1	15	17.44%
Number of prev. cesarean sections	0	76	88.37%
	1	9	10.46%
	2	1	1.16%
Number of prev. ectopic pregnancies	0	76	88.37%
	1	9	10.46%
	2	1	1.16%
Number of prev. abortions	0	67	77.9%
	1	15	17.44%
	2	2	2.32%
	3	1	1.16%
	4	1	1.16%
Abdominal pain upon admission		38	44.18%
Vaginal bleeding upon admission		67	77.9%
Free fluid in the abdomen upon admission		25	29.06%
Mean time of hospitalization (days)		9.7 ± 5.2	
Mean b-hCG upon admission (mIU/ml)		3569.8 ± 4552.9	
Mean b-hCG max (mIU/ml)		4809.3 ± 6079.4	
Mean b-hCG on discharge (mIU/ml)		2234.7 ± 3202.4	
Mean decrease of b-hCG on discharge (%)		57.5 ± 25.1	

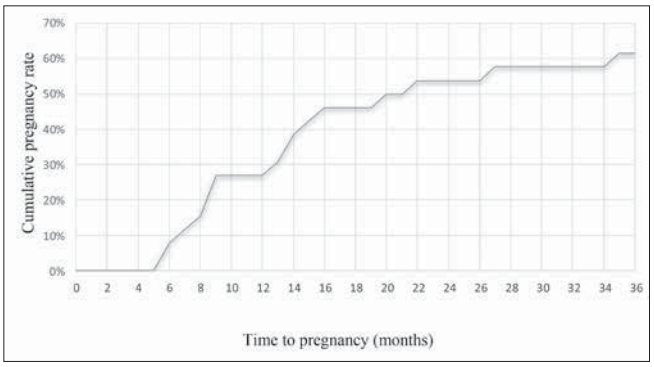

Figure 1.

Information regarding reproductive plans and possible pregnancies was obtained from 40 patients during patient follow-up visits to the outpatient clinic, as well as through telephone contact. Three months into the MTX treatment, 3 patients decided to enroll into an *in vitro* fertilization program and 2 of them gave birth to healthy children. These patients were excluded from further studies. Surgical procedures were performed in 3 other patients during MTX therapy and these patients were not included in further studies, either. Among the 34 patients that qualified for further statistical analysis, 8 (23.5%) did not attempt to conceive again, whereas 26 patients attempted to conceive again and 16 of them (61.53%) gave birth to healthy children. The average time to pregnancy was 14.9 months (SD±10.9), with the first and the last pregnancy occurring after 6 and 35 months, respectively. The cumulative pregnancy rate after a 42-month observation period post-treatment is illustrated in Figure #1. Not a single case of congenital birth defects, especially neural tube or cardiac, was observed . The average birth weight was 3425g (SD±408.3). A recurrence of ectopic pregnancy was not observed in the study population. The characteristics of patients who gave birth as well as those who, despite expectations, did not conceive are presented in Table II.

Discussion

Methotrexate remains to be the most commonly used, as well as the most effective, medication in conservative management of ectopic pregnancy. This antagonist of folic acid disrupts DNA synthesis and inhibits cell proliferation. The rapidly dividing trophoblastic tissue is especially sensitive to its effects. MTX effect on other tissues strongly depends on the dose of the drug. The most commonly encountered adverse effects of MTX overdose include inflammation of the mucosa of the gastrointestinal tract, bone marrow suppression, conjunctivitis, hepatotoxicity, and photosensitivity. Systemic administration of the medication may be used in a variety of schemes. In our study, a single dose of 50 mg MTX, without additional folic acid supplementation, was administered. In cases with insufficient drops of the b-hCG concentration, additional doses of MTX were given.

The efficacy of conservative MTX treatment was 93%. Noteworthy, the treatment was effective in patients with higher b-hCG concentrations (maximal value: 22088 mIU/ml). The number of doses of MTX and the total dose administered are presented in Table III, respectively. Such a high percentage of treatment success encourages physicians to attempt administering

Table II.

	1- pregnant 2- not pregnant	number of patients	mean	SD	min	max	p value
Hospitalization time (days)	1	15	11.7	4.1	6	18	0.06
	2	10	8.4	3.7	4	15	
First b-hCG (IU/ml)	1	16	3185.6	2688.7	58	8414	0.12
	2	10	1478	1261.6	76	3937	
Max b-hCG (IU/ml)	1	16	4404.6	3855.7	58	3425.5	0.06
	2	10	1920.4	2194.6	118	1259	
b-hCG on discharge (IU/ml)	1	15	2011.9	1638	17	5279	0.08
	2	10	1072.4	1715.6	38	5772	
Decrease of b-hCG on discharge (%)	1	15	55.4	22.9	23.4	96.1	0.85
	2	10	52.4	20.3	21.3	87.8	
BMI (kg/m2)	1	16	22.4	2.3	19.6	26.2	0.79
	2	10	22.8	4.4	18	29.2	
age (years)	1	16	28.9	4.6	22	39	0.17
	2	10	31.4	4.5	30	40	

the medication in outpatient settings, which would significantly contribute to reducing hospitalization costs. This course of action requires proper training of the medical and nursing staff at the outpatient clinic, as well as establishing specific criteria regarding administering subsequent MTX doses and recurrent hospitalization. It is also necessary to educate patients and their families so that they know how to react properly in the case of worsening complaints.

Under ideal operating conditions, a cumulative pregnancy rate similar to the one found with conservative MTX treatment was observed. Such ideal conditions can occur only in case of microsurgical reanastomosis of the fallopian tubes after a prior tubal ligation, where the cumulative pregnancy rate (including ectopic) is 62.5% [26].

In the study population subjected to MTX therapy, ectopic pregnancies were not observed. Unfortunately, microsurgeries of the fallopian tubes using the laparoscopic technique have a flat learning curve, which may result in an insufficiency of highly trained staff members, especially during emergency situations.

Fertility evaluation in patients after conservative treatment was highly satisfactory. During hospitalization, no statistical significance in the amount of the administered MTX was observed between patients with an attempted failed conception and patients with a successful pregnancy and delivery. Also, there were no significant differences between the rate of decrease of the b-hCG concentration and hospitalization length – (Pearson's correlation coefficient r=0.802). It is interesting to consider elevated b-hCG concentrations on the border of statistical significance (p=0.06) in case of patients that successfully conceived. This may be due to greater blood flow in the region of the ectopic pregnancy, thus facilitating drug absorption into the target tissue.

Table III.

Dose of Methotrexate i.m.	number of MTX dosages	number of patients	percentage of patients
50 mg	1	6	7.0%
100 mg	2	19	22.1%
150 mg	3	42	48.8%
200mg	4	6	7.0%

The presence of symptoms upon admission was on the border of significance (p=0.06) – i.e. abdominal pain and vaginal bleeding, which was more frequent in patients able to conceive spontaneously after the treatment. We suspect that one of the main factors in maintaining further fertility is localization of the ectopic pregnancy. Severe signs and symptoms may suggest an intramural section of the fallopian tube. Although a greater intensity of symptoms makes the decision for conservative treatment more difficult, MTX treatment remains to be beneficial.

It is worth to mention the emotional trauma which accompanies the diagnosis of an ectopic pregnancy. The diagnosis, and the following grief, may have an impact on the sexuality of the couple. As conservative treatment is more time consuming, patients should be offered Tender Loving Care (TLC).

Studies have shown that TLC may have a significant impact on the chance of a live birth rate in the next pregnancy [27]. We find the perspective of regaining fertility especially important to these couples.

It is also vital to note that MTX therapy is the treatment of choice in cases of unique localizations of an ectopic pregnancy, such as cervical and uterine scar pregnancies. Finally, in uncertain cases effort should be undertaken to avoid ethical consequences of the wrong diagnosis and decision.

Conclusions

Systemic, conservative management with methotrexate is an effective and safe form of treating an ectopic pregnancy, even in cases where b-hCG concentrations are greater than 3500 mIU/ml. The majority of patients can be successfully treated without surgery, and therefore may even be treated in outpatient settings.

High fertility, independent of the skills of the operators and access to laparoscopic techniques, can be maintained. Conservative treatment does not increase the risk of developing a recurrent ectopic pregnancy. Treatment should be offered in wards that provide 24-hour surgical care.

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