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CLINICAL CASE OF METHOTREXATE SIDE EFFECT

Methotrexate is a cytostatic drug from the group of folic acid antagonists, which inactivates dihydrofolate reductase and reduces the level of tetrahydrofolate, which leads to blocking of cell division and their irreversible damage. Due to this mechanism of action, methotrexate has a wide range of applications in medical practice. However, there are some risks of developing side effects, which can manifest themselves both in the form of mild symptoms, including nausea, vomiting, fever, and in the form of severe conditions with myelosuppression and pancytopenia. This article reflects a clinical case of a side effect of methotrexate when it is used in gynecological practice for the purpose of conservative treatment of a patient with an intact tubal pregnancy.

The aim of the study. *To analyze a clinical case of the use of methotrexate in gynecological practice for the treatment of damaged tubal disease, and its side effects.*

Materials and methods. *The medical history of a patient with an intact tubal pregnancy, who was administered methotrexate with the appointment of conservative treatment, was analyzed.*

Results and discussion. *This article reflects a clinical case of a side effect of methotrexate when it is used in gynecological practice for the purpose of conservative treatment of a patient with an intact tubal pregnancy. On the 3rd day after the administration of the second dose of methotrexate, the patient developed manifestations of urticaria, pharyngitis, stomatitis, agranulocytosis, hyperthermia. A consultation of doctors diagnosed a side effect of methotrexate. Over the following weeks, the patient's condition gradually worsened: pancytopenia increased, pneumonia developed, and secondary skin lesions appeared.*

Conclusions. *Only an individual approach to each patient, taking into account all clinical symptoms and monitoring the general condition and hemostasis indicators, will allow timely detection of side effects of the drug. Timely correction of changes in the general condition will allow achieving complete recovery of the patient.*

Key words: *methotrexate, side effect, intact tubal pregnancy, myelosuppression, cytopenic syndrome, skin lesions.*

Валентин Потапов, Ірина Гарагуля, Ольга Черкасова, Ганна Гарагуля, Тетяна Василенко, Юлія Нурієва. КЛІНІЧНИЙ ВИПАДОК ПОБІЧНОЇ ДІЇ МЕТОТРЕКСАТУ

Метотрексат – цитостатичний препарат із групи антагоністів фолієвої кислоти, який інактивує дигідрофолатредуктазу і знижує рівень тетрагідрофолату, що призводить до блокування поділу клітин та їх незворотного пошкодження.

Зважаючи на даний механізм дії, метотрексат має широкий спектр застосування в медичній практиці. Проте існують деякі ризики розвитку побічних ефектів, які можуть проявлятися як у вигляді легких симптомів, які включають

нудоту, блювання, підвищення температури тіла, так і у вигляді тяжких станів з мієлосупресією та панцитопенією. Дана стаття висвітлює клінічний випадок побічної дії метотрексату при його застосуванні в гінекологічній практиці з метою консервативного лікування пацієнтки з непорушеною трубною вагітністю.

Мета дослідження. *Проаналізувати клінічний випадок застосування метотрексату в гінекологічній практиці для лікування непорушеної трубної вагітності, та його побічну дію.*

Матеріали та методи. *Проаналізовано історію хвороби пацієнтки з непорушеною трубною вагітністю, якій застосовували метотрексат у консервативному лікуванні.*

Результати та обговорення. *У статті відображено клінічний випадок побічної дії метотрексату при його застосуванні в гінекологічній практиці з метою консервативного лікування пацієнтки з непорушеною трубною вагітністю. На 3 добу після введення другої дози метотрексату у хворого з'явилися прояви кропив'янки, фарингіту, стоматиту, агранулоцитозу, гіпертермії. На консиліумі лікарів встановлено побічну дію метотрексату. Протягом наступних тижнів стан хворої поступово погіршувався: наростала панцитопенія, розвивалася пневмонія, з'являлися вторинні ураження шкіри.*

Висновки. *Тільки індивідуальний підхід до кожного пацієнта, врахування всіх клінічних симптомів і моніторинг загального стану і показників гемостазу дозволить вчасно виявити побічну дію препарату. Своєчасна корекція змін загального стану дозволить домогтися повного одужання пацієнта.*

Ключові слова: *метотрексат, побічна дія, непорушена трубна вагітність, мієлосупресія, цитопенічний синдром, ураження шкіри.*

Methotrexate is a cytostatic drug from the group of folic acid antagonists [6]. The main mechanism of action of methotrexate is provided by the antifolate properties of the drug. In the human body, folic acid is broken down by the enzyme dihydrofolate reductase to form metabolically active products of dihydrofolic and tetrahydrofolic acids, which participate in the conversion of homocysteine to methionine, the formation of purines and thymidylate, which are necessary for DNA synthesis. Methotrexate inactivates dihydrofolate reductase, which leads to a decrease in the level of tetrahydrofolate, blocking cell division and their irreversible damage [3, 5].

This mechanism of action allows the use of methotrexate for the treatment of oncological, autoimmune, dermatological diseases, as well as the prescription of the drug in gynecological practice [1].

Although the effectiveness of methotrexate treatment is quite high (according to many sources, it ranges from 70-90%), some patients cannot use it due to the development of side effects [2]. The severity of side effects depends on the dose and duration of treatment. The following symptoms are most often observed: increased body temperature, nausea, vomiting, stomatitis, mucositis. Also, the use of methotrexate is associated with hepatotoxicity and a short-term increase in liver enzymes (ALT, AST), which disappears after the end of the course of treatment. Rare side effects include myelosuppression followed by pancytopenia, alopecia and pneumonia [7].

Therefore, in view of the above-mentioned side reactions, contraindications for the use of methotrexate are immunodeficiency states, moderate and severe anemia, leukopenia, thrombocytopenia, lung diseases, peptic ulcer disease of the stomach and duodenum, kidney or liver failure [4].

This article presents a clinical case of the side effect of methotrexate when using this drug in gynecological practice for the purpose of conservative treatment of ectopic pregnancy. Therapy for this case was carried out in accordance with the current Standards of Medical Care «Ectopic Pregnancy», approved by the Order of the Ministry of Health of Ukraine dated September 24, 2022, № 1730 [8]. Currently, the following criteria for the possibility of using methotrexate have been implemented:

- hemodynamic stability of the patient;
- progressive tubal pregnancy measuring less than 35 mm without visible fetal heartbeat on ultrasound;
- absence of intrauterine pregnancy on ultrasound;
- serum β-hCG level from < 1500 IU/L to < 5000 IU/L;
- patient consent to further medical observation, no known sensitivity to methotrexate.

Clinical case. Patient O., born in 1997, was hospitalized in the gynecology department due to an intact tubal pregnancy on the left. The diagnosis was confirmed by the results of pelvic ultrasound (diffuse changes in the myometrium, ectopic pregnancy on the left, left ovarian cyst) and the β-hCG level (3820 IU/L). The patient refused surgical treatment. Due to the β-hCG level, the patient's hemodynamic stability, the absence of a heartbeat and an uterine pregnancy according to pelvic ultrasound data, a decision was made to carry out conservative treatment using methotrexate at a dose of 50 mg/m2 [8]. The drug was administered intramuscularly at a dosage of 75 mg. Therapy was monitored on the 4th day after the first administration of methotrexate: β-hCG – 3520 IU/L, according to pelvic ultrasound data – a formation in the small pelvis on the left. Given the insufficient reduction in the β-hCG level (<15%), a decision was made to re-administer methotrexate at a dosage of 75 mg in accordance with the Standards of Medical Care [8].

On the 3rd day after the administration of the second dose of methotrexate, the patient complained of an increase in body temperature to 38.2°C, general weakness, sore throat, skin rash on the neck and upper chest, itching, and minor bloody discharge from the genital tract.

On the 4th day after the second dose of methotrexate, the patient's complaints persist; a general blood test shows anemia (Hb – 79 g/l, E – $3.06*10^{12}$/l) and leukopenia (L – $2.0*10^{9}$/l). Based on the results of the consultation, which included an allergist, dermatovenerologist, infectious disease specialist, otolaryngologist and therapist, the diagnosis was established: Tubal pregnancy (intact). Side effects of methotrexate with manifestations of urticaria, pharyngitis, stomatitis, agranulocytosis, hyperthermia.

The patient was transferred to the intensive care unit. Recombinant human granulocyte colony-stimulating factor – filgrastim (Zarzio), FFP, Albumin, Dexamethasone, Nolpaza, Biseptol and symptomatic treatment were prescribed. Recommended crushed homogeneous food or baby food.

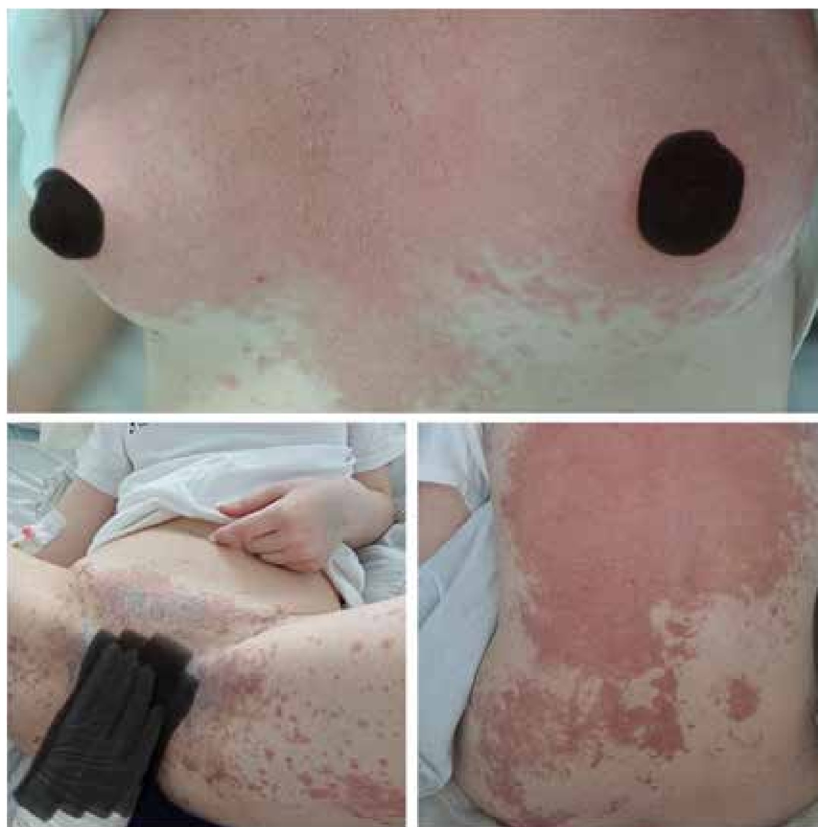
On the 5th day after the second dose of methotrexate, the patient's condition is severe, thrombocytopenia has appeared (T – from $142*10^{9}$/l to $53*10^{9}$/l). A consultation with a hematologist was conducted. Additionally, platelet mass was prescribed.

Diagnosis: Tubal pregnancy (non-excited). Condition after methotrexate treatment. Secondary cytopenic syndrome in the form of severe leukopenia, severe anemia, severe thrombocytopenia without hemorrhagic manifestations. Mucositis. Aphthous stomatitis. Pharyngodynia. Enteropathy. Secondary skin lesion.

Sternal puncture was performed. Correction of the prescribed therapy: Meropenem, Vancomycin, Fluconazole, Zarzio, Erythrocyte mass, Platelet concentrate, hemostatic therapy.

On the 7th day after the second dose of methotrexate – the general condition of the patient worsens, the spread of confluent rashes to the scalp, back, shoulders, buttocks, perineum. The oral cavity is treated with Atoxil powder and 0.05% Chlorhexidine solution, the skin and external genitalia are sanitized.

Over the next two weeks, the patient's condition is stable and severe, complaints of thirst, burning pain in the mouth, tightness of the skin of the face, neck, anterior chest, painful sensations in the area of the external genitalia, hair loss, periodic minor serous-bloody discharge from the genital tract. During an objective examination, the border of the lips is hyperemic, there are painful erosions on the lips covered with crusts, under the tongue, in the oral cavity, on the upper surface of the tongue there are multiple aphthae, desquamation of the tip of the tongue. The rash on the skin of the face, trunk, in the perineum area persists. In some places, the skin peels. Alopecia of the scalp. In the general blood test, a marked decrease in the indicators remains: severe anemia with hypochromia and anisopoikilocytosis (Hb – 69 g/l, E – $2.6*10^{12}$/l), leukopenia (L – $0.9*10^{9}$/l), thrombocytopenia



Pic. 1. Confluent rash on the patient's torso

(T – $24*10^9$/l), accelerated ESR (12 mm/h). According to the ECG results – NLBBB, signs of LVH, ischemia in the lower lateral and apical areas, short QT syndrome. The scope of therapy remains the same: stimulation of leukopoiesis (Zarzio), transfusion of FFP, erythrocytes, platelets, antibacterial (Gepacef combi + Levofloxacin), antifungal (Fluconazole), detoxification, metabolic, gastro- and hepatoprotective therapy. Treatment of the skin with Panthenol solution. Treatment of the oral cavity. Treatment of the vagina with antiseptics, turundas with antiseptics.

On the 23rd day after the second dose of methotrexate, a consultation with a chemotherapist was conducted. During an objective examination, a hematoma of the left eye was noted. During auscultation, breathing was produced on both sides, with a hard shade, weakened on the back surface in the lower sections.

Diagnosis: Tubal pregnancy (non-excited). Adverse effect of methotrexate. Secondary cytopenic syndrome in the form of severe leukopenia, severe anemia, severe thrombocytopenia with hemorrhagic syndrome. Mucositis. Aphthous stomatitis. Pharyngodynia. Enteropathy. Secondary skin lesion. NLBBB. Short QT syndrome. Right-sided lower lobe segmental pneumonia.

The treatment was adjusted – Solu-Medrol, Eltrombopag were prescribed and Zarzio was changed to Filstim. Consultation with an ophthalmologist. During the ophthalmological examination, a slight swelling of the eyelids was found, erosions in the upper corners. In the left eye, erosions on the eyelids in the outer and inner corners, a small amount of purulent discharge. Hemorrhage and swelling of the eyelids.

Diagnosis: Acute blepharitis of the left eye, hematoma of the lower eyelid of the left eye, hemorrhage OS.

On the 26th day after the second dose of methotrexate, a gradual decrease in leukopenia and the appearance of band and segmented forms in the general blood test are observed. In the biochemical blood test – hypokalemia, hyponatremia, hypomagnesemia, hypochloremia, hypoproteinemia, increased ALT activity, increased alpha-amylase levels. The appearance of symptomatic arterial hypertension and steroid-induced hyperglycemia.

Over the next two weeks, a gradual dynamic improvement in the patient's general condition is observed – a decrease in the area of confluent rashes, hematoma of the lower eyelid of the left eye and hemorrhage OS, crusting of erosions on the mucous membranes. The level of indicators in the general blood test and biochemistry increases. The above-mentioned therapy continues. Treatment of the external genitalia is carried out with vaginal gels (active ingredients – colloidal silver, sodium hyaluronate, aloe vera gel, calendula officinalis flower extract, centella asiatica herb extract, D-panthenol, lysozyme hydrochloride, epigallocatechin, tea tree essential oil, lactic acid).

On the 47th day after the second dose of methotrexate, the patient's general condition was satisfactory. The doctors' council decided to transfer her to the gynecological department.

Final diagnosis: Adverse effect of methotrexate. Secondary cytopenic syndrome in the form of severe leukopenia, severe anemia, severe thrombocytopenia with hemorrhagic syndrome. Mucositis. Aphthous stomatitis. Pharyngodynia. Enteropathy. Secondary skin lesion. NLBBB. Short QT syndrome. Right-sided lower lobe segmental pneumonia. Acute blepharitis of the left eye, hematoma of the lower eyelid of the left eye, CC hemorrhage OS. Symptomatic arterial hypertension. Steroid-induced hyperglycemia.

Conclusions. At the current stage of treatment, the use of methotrexate is an important direction in the

Table 1

Indicators of general blood analysis in dynamics

Indicator	I dose MTX	II dose MTX	4th day	11th day	17th day	19th day	22th day	25th day	32th day	35th day	42th day	45th day
Leukocytes	4,91	6,68	2,0	0,6	0,9	1,1	0,41	1,0	11,7	13,5	11,0	8,7
Erythrocytes	3,98	3,88	3,06	3,27	2,6	2,9	2,42	1,77	3,55	3,78	3,17	3,09
Hemoglobin	104	90	79	86	69	83	63	49	107	116	98	97
ESR	15	24	18	15	12	25	30	70	11	10	6	12
Granulocytes	70	67,4	35	6,2	1	1	24,5	63	72	73	80	47
Blasts	-	-	-	-	-	-	-	-	2	-	-	-
Myelocytes	-	-	-	-	-	-	-	-	4	-	2	-
Juvenile	-	-	-	-	-	-	-	-	-	-	-	-
Band	2	4	2	-	-	-	-	8	8	8	8	9
Segmented	64	63,4	33	4	1	1	24,5	55	60	65	70	38
Eosinophils	4	-	-	2	-	-	-	-	-	-	-	-
Monocytes	5	5,0	2	1	1	2	24,9	8	4	5	6	4
Lymphocytes	25	27,6	57	84,8	98	97	50,6	29	21	22	14	40
Thrombocytes	340	258	228	53	24	47	57	39	48	39	91	160

Table 2

Blood biochemistry indicators in dynamics

Indicator	I dose MTX	19th day	45th day
ALT	20,7	23,6	28,4
AST	26,6	23,2	27,4
Total bilirubin	20,1	16,1	11,0
Creatinine	57	63	57
Urea	4,4	5,4	4,11

Table 3

Coagulogram indicators in dynamics

Indicator	I dose MTX	3th day	11th day	17th day	32th day
Prothrombin time	11,9	11,3	13,8	14,1	13,7
Prothrombin index	100	106	87	85	98
Recalcification time	82	85	108	110	74
Plasma fibrin	3,55	3,33	3,20	4,20	3,0
INR	1,00	0,94	1,22	1,2	1,20

therapy of many diseases, in particular, in conservative and complex treatment of ectopic pregnancy. However, when prescribing methotrexate as a basic drug, it is necessary to take into account the possibility of developing side effects. In one case, side effects can have a mild course in the form of increased body temperature, nausea and vomiting, and otherwise they can manifest as severe cytopenic syndrome. Therefore, it is imperative to carefully weigh the risks of possible side effects of methotrexate and the expected therapeutic effect.

Before starting treatment, a complete blood count should be performed to determine the level of hemoglobin, leukocytes and platelets, as well as the level of ALT, AST, bilirubin, creatinine and urea. Further review of clinical analyses should be performed during immediate methotrexate therapy and several days and weeks after completion. The development of severe side effects requires careful daily monitoring of the patient with the selection of correct therapy.

Only an individual approach to each patient, taking into account all clinical symptoms and monitoring the general condition and hemostasis indicators, will allow timely detection of side effects of the drug. Timely correction of changes in the general condition will allow achieving complete recovery of the patient.

Література:

1. Alamo M., Grisanti M. Methotrexate in rheumatoid arthritis. *Rev. Med. Chil.* 1991. № 119. P. 691–700.
2. Bannwarth B., Schaeverbeke T., Labat L., Marce S., Demotes-Mainard F., Dehais J. Side-effects during treatment of rheumatoid arthritis with methotrexate. *Rev. Rhum. Ed.* 1994. № 61. P. 337–342.
3. Brady P. C. New Evidence to Guide Ectopic Pregnancy Diagnosis and Management. *Obstet. Gynecol. Surv.* 2017. № 72. P. 618–625. doi: 10.1097/OGX.0000000000000492.
4. Braun J., Rau R. An update on methotrexate. *Curr. Opin. Rheumatol.* 2009. № 21. P. 216–223. doi: 10.1097/BOR.0b013e328329c79d.
5. Li C., Zhao W.-H., Zhu Q., Cao S.-J., Ping H., Xi X., Qin G.-J., Yan M.-X., Zhang D., Qiu J., et al. Risk Factors for Ectopic Pregnancy: A Multi-Center Case-Control Study. *BMC Pregnancy Childbirth.* 2015. №15. P.187. doi: 10.1186/s12884-015-0613-1.
6. Marion L. L., Meeks G. R. Ectopic Pregnancy: History, Incidence, Epidemiology, and Risk Factors. *Clin. Obstet. Gynecol.* 2012. № 55. P. 376–386. doi: 10.1097/GRF.0b013e3182516d7b.
7. Sáenz Abad D., Ruiz-Ruiz F.J., Monón Ballarín S., Mozota Duarte J., Marquina Barcos A. Pneumonitis associated to methotrexate. *An. Med. Interna.* 2008. № 25. P. 27–30. doi: 10.4321/s0212-71992008000100007.
8. Про затвердження Стандартів медичної допомоги «Ектопічна вагітність», Наказ МОЗ України № 1730, 24 вер. 2022. URL: https://www.dec.gov.ua/wp-content/uploads/2022/09/40273-dn_1730_24092022_dod.pdfr