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ANALYSIS OF THE RESULTS OF CONSERVATIVE MANAGEMENT OF ECTOPIC PREGNANCY USING METHOTREXATE

Abstract. *Today, ectopic pregnancy remains a common gynecological emergency around the world and is defined as the implantation of a fertilized egg outside the uterine cavity. The fallopian tube is the most common site of attachment of the fertilized egg, and tubal pregnancies account for 95.5% of all cases of ectopic pregnancy. Taking into account modern practice, two methods of treating tubal pregnancy can be noted – conservative with the use of methotrexate and surgical. And although conservative management of this pathology is 70–90% effective and safe, in Ukraine the frequency of use of this drug does not exceed 15%. The presented article highlights modern recommendations for the use of methotrexate for the treatment of tubal pregnancy and directly analyzes the results of conservative management of women with undisturbed tubal pregnancy in the department of planned minimally invasive and plastic gynecology of subdivision № 3 of the KNP "City Clinical Hospital № 6".*

The aim of the study. *The purpose of the study is to analyze the results and determine the features of managing patients with intact tubal pregnancy using methotrexate.*

Materials and methods. *We analyzed 49 cases of treatment of tubal pregnancy with methotrexate in hemodynamically stable patients of the department of planned minimally invasive and plastic gynecology of subdivision № 3 of the KNP "City Clinical Hospital № 6" for 2020–2022. A systematic online study of articles on the use of methotrexate was conducted.*

Results and discussion. *Drug treatment of tubal pregnancy with methotrexate was used in 49 women (31.4%) out of 156 who were hospitalized with a diagnosis of ectopic pregnancy. All patients met the established requirements for conservative management of ectopic pregnancy. The average age of women in the study group was 22.3 ± 3.5 years.*

In the obstetric history, the first pregnancy was identified in 31 patients (63.3%), repeated pregnancy – in 18 patients (36.7%). In women with repeated pregnancies, physiological births accounted for 66.7% (12 cases), cesarean sections – 33.3% (6 cases). Two or more births were detected in 4 patients (22.2%). Abortions occurred in 10 women with repeat pregnancies (55.6%).

Primary infertility was detected in 9 women (18.4%), secondary infertility – in 1 woman (2.0%). Regular menstrual cycle disorders of various types were observed in 17 patients (34.7%). 5 women (10.2%) had chronic inflammatory processes of the pelvic organs. Combined oral contraceptives were used as a method of contraception by 1 woman (2%).

Preliminary surgical interventions on the pelvic organs were performed in 11 women (22.4%) with conservative management of tubal pregnancy. Of these, the indications for surgical intervention were: genital endometriosis – in 2 patients (18.2%), ectopic pregnancy – in 5 patients (45.5%), tubo-peritoneal factor of infertility – in 4 patients (36.3%). In 2 patients (40%) with a previously operated tubal pregnancy, the fallopian tube was preserved. In 1 patient (50%), this ectopic pregnancy was diagnosed in a preserved fallopian tube.

7 patients (14.3%) had chronic diseases of the urinary system.

A single injection of the drug at a rate of 50 mg/m2 of body surface was performed in 41 women (83.7%), repeated administration was used in 8 women (16.3%).

Surgical treatment with progression of tubal pregnancy was performed in 7 women (14.3%).

Conclusions. *The use of methotrexate during conservative therapy for tubal pregnancy in the department of planned minimally invasive and plastic gynecology of subdivision № 3 of the KNP "City Clinical Hospital № 6" allowed to avoid surgical intervention and preserve reproductive function and health in 85.7% of women.*

Key words: *ectopic pregnancy, tubal pregnancy, methotrexate, complications, conservative treatment.*

АНАЛІЗ РЕЗУЛЬТАТІВ КОНСЕРВАТИВНОГО ЛІКУВАННЯ ЕКТОПІЧНОЇ ВАГІТНОСТІ ІЗ ЗАСТОСУВАННЯМ МЕТОТРЕКСАТУ

Анотація. *На сьогоднішній день ектопічна вагітність залишається розповсюдженою невідкладною гінекологічною патологією у всьому світі і визначається як імплантація плідного яйця за межами порожнини матки. Маткова труба є найчастішим місцем прикріплення плідного яйця, а трубна вагітність складає 95,5% від усіх випадків позаматкової вагітності. З огляду на сучасну практику можна зазначити два методи лікування трубної вагітності – консервативний із застосуванням метотрексату та хірургічний. І хоча консервативне ведення даної патології є ефективним і безпечним на 70–90%, в Україні частота застосування даного препарату не перевищує 15%. Представлена стаття висвітлює сучасні рекомендації застосування метотрексату з метою лікування трубної вагітності та безпосередньо аналізує результати консервативного ведення жінок з непорушеною трубною вагітністю у відділенні планової малоінвазивної та пластичної гінекології підрозділу № 3 КНП «МКЛ № 6» ДМР.*

Мета дослідження. *Метою дослідження є аналіз результатів та визначення особливостей ведення пацієнток з непорушеною трубною вагітністю за допомогою метотрексату.*

Матеріали та методи дослідження. *Проаналізовано 49 випадків лікування трубної вагітності метотрексатом у гемодинамічно стабільних пацієнток відділення планової малоінвазивної та пластичної гінекології підрозділу № 3 КНП «МКЛ № 6» ДМР за 2020–2022 рр. Проведено систематичне онлайн-дослідження статей на тему застосування метотрексату при трубній позаматковій вагітності.*

Результати і обговорення. *Медикаментозне лікування трубної вагітності метотрексатом застосовувалося у 49 жінок (31,4%) із 156, які були госпіталізовані до стаціонару із діагнозом позаматкова вагітність. Усі пацієнтки відповідали встановленим вимогам до консервативного ведення позаматкової вагітності. Середній вік жінок досліджуваної групи становив 22,3 ± 3,5 років.*

В акушерському анамнезі перша вагітність встановлена у 31 пацієнтки (63,3%), повторна вагітність – у 18 пацієнток (36,7%). У жінок із повторною вагітністю фізіологічні пологи складали 66,7 % (12 випадків), кесарів розтин – 33,3% (6 випадків). Двоє і більше пологів визначались у 4 пацієнток (22,2%). Аборти мали місце у 10 жінок із повторною вагітністю (55,6%).

Первинне безпліддя встановлено у 9 жінок (18,4%), вторинне безпліддя – у 1 жінки (2,0%). Регулярні порушення менструального циклу різного характеру спостерігалися у 17 пацієнток (34,7%). Хронічні запальні процеси органів малого тазу мали 5 жінок (10,2%). Комбіновані оральні контрацептиви, як метод контрацепції, застосовувала 1 жінка (2%).

Попередні оперативні втручання на органах малого тазу виконано у 11 жінок (22,4%) з консервативним веденням трубної вагітності. З них показаннями до оперативного втручання були: генітальний ендометріоз – у 2 пацієнток (18,2%), позаматкова вагітність – у 5 пацієнток (45,5%), трубно-перитонеальний фактор безпліддя – у 4 пацієнток (36,3%). У 2 пацієнток (40%) із попередньо прооперованою трубною вагітністю збережено маткову трубу. У 1 пацієнтки (50%) дана позаматкова вагітність діагностована у збереженій матковій трубі.

У 7 пацієнток (14,3%) спостерігалися хронічні захворювання сечовидільної системи.

Одноразове введення препарату з розрахунку 50 мг/м^2 поверхні тіла було виконано у 41 жінки (83,7%), повторне введення було застосоване у 8 жінок (16,3%).

Оперативне лікування з прогресуванням трубної вагітності було проведено у 7 жінок (14,3%).

***Висновки.** Застосування метотрексату при проведенні консервативної терапії з приводу трубної вагітності у відділенні планової малоінвазивної та пластичної гінекології підрозділу № 3 КНП «МКЛ № 6» ДМР дозволило уникнути оперативного втручання та зберегти репродуктивну функцію і здоров'я у 85,7% жінок.*

***Ключові слова:** ектопічна вагітність, трубна вагітність, метотрексат, ускладнення, консервативне лікування.*

Introduction. An urgent problem of modern obstetrics and gynecology is the high prevalence of ectopic pregnancy among women of reproductive age. Thus, according to Milena Leziak, Klaudia Zak, Karolina Frankowska (2022), the prevalence of ectopic pregnancy among pregnant women reaches up to 2%. Ectopic pregnancy is the main cause of maternal mortality in the first trimester of pregnancy and accounts for 5–10% of all pregnancy-related deaths. This is due to the difficulty of timely diagnosis of ectopic pregnancy associated with a nonspecific clinical picture [1–3; 10].

There is also a steady trend towards an increase in the frequency of ectopic pregnancy, which in industrialized countries averages 12–14 cases per 10,00 pregnancies [2]. Moreover, tubal pregnancy accounts for 95.5% of all locations of ectopic pregnancy. Infertility after surgery for tubal pregnancy can occur in 70–80% of cases. The frequency of repeated tubal pregnancy is observed in the range from 4 to 12.6% [3]. First of all, this is due to the prevalence of inflammatory processes in the female genital organs, the increasing number of surgical interventions on the fallopian tubes, and the introduction of ovulation inducers into medical practice [3].

The diagnostic capabilities of modern medicine make it possible in most cases to establish a diagnosis of tubal pregnancy before its termination, thereby reducing the risk of life and reproductive health of the patient and increasing the range of possible treatment methods [9].

Today, in parallel with laparoscopic manipulations, conservative medical methods are used in the treatment of tubal pregnancy. Their essence consists in the systemic or local use of drugs by introducing the drug into the fetal sac during laparoscopy or under ultrasound guidance.

The most studied drug for the medical treatment of ectopic pregnancy is methotrexate. The first use of methotrexate occurred in 1982 with interstitial localization of the ovum [8]. From that moment on, its use has firmly taken its place in the treatment of this pathology.

A review of uncontrolled and controlled studies found that when patients are stable, there are many drug treatments that are as effective as surgery. Moreover, in different studies, the success rate with methotrexate therapy ranged from 71.2 to 97% [6]. The success of the method depends on the mode of application, gestational age, diameter of the ovum and the level of human chorionic gonadotropin.

At the moment, the following criteria for the possibility of using methotrexate have been approved in Ukraine:

- hemodynamic stability of the patient;
- progressive tubal pregnancy less than 35 mm in size without visible fetal heartbeat on ultrasound;
- absence of uterine pregnancy on ultrasound;
- serum level of human chorionic gonadotropin from < 1500 IU/l to < 5000 IU/l;
- the patient's consent to further medical observation;
- absence of known sensitivity to methotrexate [7].

The aim of the study. The purpose of the study was to analyze the results and determine the characteristics of the management of patients with an intact tubal pregnancy with the help of methotrexate in the department of planned minimally invasive and plastic gynecology of subdivision № 3 of the KNP "City Clinical Hospital № 6".

Materials and methods. We analyzed 49 cases of intact tubal pregnancy with methotrexate in patients of the department of planned minimally invasive and plastic gynecology of subdivision № 3 of the KNP "City Clinical Hospital № 6". When choosing a treatment method, a number of factors were taken into account: the patient's condition, gestational age, life history, medical history, ultrasound results.

The criteria for medical treatment of ectopic pregnancy in patients were: hemodynamic stability, progressive tubal pregnancy measuring less than 35 mm without visible fetal heartbeat on ultrasound, absence of intrauterine pregnancy on ultrasound, serum level of human chorionic gonadotropin from

< 1500 IU/l to < 5000 IU/l, the patient's consent to further medical observation, absence of known sensitivity to methotrexate [7].

Before choosing management tactics, all patients were examined by a council of doctors and general examination, ultrasound examination, general clinical blood test were performed, and the level of human chorionic gonadotropin in the blood was determined. For conservative treatment of intact tubal pregnancy, methotrexate was used. This is a cytostatic drug from the group of folic acid antagonists. The mechanism of action is the inactivation of dihydrofolate reductase, which leads to a decrease in the level of tetrahydrofolate (cofactor for DNA and RNA synthesis) and thereby blocks the division of trophoblast cells. The dose of the drug was determined at the rate of 50 mg/m^2 on the body surface. When repeated administration, the dosage of the drug did not change. Monitoring of human chorionic gonadotropin levels and ultrasound control were carried out 96 and 168 hours after methotrexate administration [7].

The results obtained were subjected to statistical processing using the method of descriptive statistics and correlation analysis.

Results and discussion. Drug treatment of tubal pregnancy with methotrexate was used in 49 women (31.4%) out of 156 who were hospitalized with a diagnosis of ectopic pregnancy. All patients met the established requirements for conservative management of ectopic pregnancy. The average age of women in the study group was 22.3 ± 3.5 years.

In the obstetric history, the first pregnancy was identified in 31 patients (63.3%), repeated pregnancy – in 18 patients (36.7%). In women with repeated pregnancies, physiological births accounted for 66.7% (12 cases), cesarean sections – 33.3% (6 cases). Two or more births were detected in 4 patients (22.2%). Abortions occurred in 10 women with repeat pregnancies (55.6%).

When collecting anamnesis, it was established that in the patients of the study group, menarche occurred at 13.2 ± 1.2 years. Primary infertility was detected in 9 women (18.4%), secondary infertility – in 1 woman (2.0%). Regular menstrual cycle disorders of various types were observed in 17 patients (34.7%). 5 women (10.2%) had chronic inflammatory processes of the pelvic organs. Combined oral contraceptives were used as a method of contraception by 1 woman (2%).

Preliminary surgical interventions on the pelvic organs were performed in 11 women (22.4%) with conservative management of tubal pregnancy. Of these, the indications for surgical intervention were: genital endometriosis – in 2 patients (18.2%), ectopic pregnancy – in 5 patients (45.5%), tubo-peritoneal factor of infertility – in 4 patients (36.3%). In 2 patients (40%) with a previously operated tubal pregnancy, the fallopian tube was preserved. In 1 patient (50%), this ectopic pregnancy was diagnosed in a preserved fallopian tube.

Analyzing extragenital diseases, it was found that 7 patients (14.3%) had chronic diseases of the urinary system. Other diseases were isolated and not statistically significant.

When using methotrexate, some peculiarities have been established. A single injection of the drug at a rate of 50 mg/m^2 of body surface was performed in 41 women (83.7%), repeated administration was used in 8 women (16.3%). The condition for repeat administration of methotrexate 168 hours after the first administration was an increase in plasma human chorionic gonadotropin levels above the baseline level or its decrease by less than 15% [7]. The use of the drug was accompanied by a number of side effects. The duration of side effects depends on the dose and duration of treatment with methotrexate. Side effects with one dose of the drug were usually minor and stopped quickly.

The average hospital stay was 8.7 ± 1.3 days. All patients were discharged in satisfactory condition under the supervision of an obstetrician-gynecologist in the antenatal clinic with recommendations.

Surgical treatment with progression of ectopic pregnancy was performed in 7 women (14.3%). In 2020, out of 15 women, 4 women were operated on (26.7%), in 2021, out of 14 women, 2 women were operated on (14.3%), in 2022, out of 20 women, 1 woman was operated on (0.5%) which indicates a trend towards a decrease in the number of surgical interventions when using methotrexate for the treatment of intact tubal pregnancy.

At the same time, the scheme of single and repeated administration of methotrexate was more appropriate compared to surgical intervention. This is due to a reduction in the costs of hospitalization, surgery and rehabilitation, since in the early stages of this pathology it is possible to manage patients in a day hospital or a one-day hospital stay with monitoring of ultrasound and the level of human chorionic gonadotropin in the blood. Indirect costs are reduced by reducing downtime.

Conclusions. Conservative treatment of intact tubal pregnancy is controversial due to the possibility of complications and the need for surgical intervention. The study indicates that compliance with the criteria for selecting patients for the purpose of prescribing methotrexate, timely ultrasound examination, determination of the level of human chorionic gonadotropin in the blood plasma and the use of a second dose of the drug, if necessary, allows one to avoid surgical intervention, preserve the fallopian tube and reduce the cost of treatment.

The use of methotrexate during conservative therapy for tubal pregnancy in the department of planned minimally invasive and plastic gynecology of subdivi-

sion № 3 of the KNP "City Clinical Hospital № 6" made it possible to prevent surgical intervention in 85.7% of women and preserve reproductive function and health.

Currently, methotrexate is the drug of choice for the conservative management of tubal pregnancy and is a safe alternative to surgical treatment.

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