

Pharmalogical treatment of ectopic pregnancy

Joanna Habaj (BCDEF), Adam Dyrda(A), Marlena Wojnarowska (BCDEF)

Department Obstetrics and Gynecology with the Oncological Gynecology at Szpital Wojewódzki MEGREZ Sp. z o.o. in Tychy, Poland

AUTHORS' CONTRIBUTION: (A) Study Design · (B) Data Collection · (C) Statistical Analysis · (D) Data Interpretation · (E) Manuscript Preparation · (F) Literature Search · (G) Funds Collection

SUMMARY

Introduction. Ectopic pregnancy is the result of inappropriate embryo implantation affecting 1 -2 % of pregnancies. The frequency of this pathological form of pregnancy has been on the same level for years and still constitutes one of the most common causes of women's death in childbearing age in undeveloped countries.

Aim. The aim of the study was to assess the diagnosis of early ectopic pregnancy in potential childbearing patients and their qualification for methotrexate (MTX) treatment.

Material and methods. The analysis includes patients of the Szpitala Powiatowego Centrum Zdrowia in Mikołów in the years 2007 – 2017. Diagnosis of the ectopic pregnancy included a detailed history interview with highlighted chorionic gonadotropin combined with physical examination and assessment in transvaginal ultrasound examination. After observational study at women with confirmed early ectopic pregnancy, whose health and other factors weren't a contraindication pharmacological method for methotrexate treatment in dose of 1mg/kg body weight was introduced. The Patients were informed about the treatment method, possible side effects and alternative treatments. They expressed informed consent for drug treatment. The necessity of second dose injection with methotrexate was not considered as a treatment failure. Women, from with various reasons couldn't be included in the methotrexate treatment protocol, they were qualified to surgical proceedings, whose the dominant procedure was laparoscopy. Urgent laparotomy was performed in case of danger to life.

Results. The analysis included 134 patients with diagnosed ectopic pregnancy within 10 years (2007 – 2017). A medical protocol of methotrexate treatment was used with 39 patients, of which 35 achieved complete remission, which accounts for 90% of those reported cases. Good drug tolerance was observed. The most common reported side effects symptoms include: general weakness, abdominal pain, nausea, diarrhea.

Conclusion. The study shows that the level of chorionic gonadotropin and transvaginal ultrasound examination is a qualifying factor in early ectopic pregnancy for methotrexate treatment. It has also been shown that the therapy has a high effectiveness which can help to avoid surgical treatment.

Key words: ectopic pregnancy; methotrexate; chorionic gonadotropin; transvaginal ultrasound examination; laparoscopy

Address for correspondence:

Joanna Habaj – Department Obstetrics and Gynecology with the Oncological Gynecology at Szpital Wojewódzki MEGREZ Sp. z o.o. w Tychach, ul. Edukacji 102, 43-100 Tychy

Word count: 1434 **Tables:** 1 **Figures:** 3 **References:** 12

Received: 08.03.2020

Accepted: 18.03.2020

Published: 31.03.2020

INTRODUCTION

Ectopic pregnancy is the result of inappropriate embryo implantation affecting 1 -2% of pregnancies [1]. The frequency of this pathological form of pregnancy has been on the same level for years and still constitutes one of the most common causes of women's death in childbearing age in undeveloped countries [2]. The difficulty in the diagnosis of the abovementioned condition lies in uncharacteristic symptoms such as: no period, bleeding from birth canal, pain and tenderness in under belly area. The above triad of symptoms occurs with 45% of patients. Some of them may not present any symptoms at all. The pregnancy developing in a Fallopian tube may lead to its breaking, which will manifest itself with sudden, diffuse pain in the abdominal area and hypovolemic shock, which may require immediate surgical intervention [3]. The enumerated symptoms require differentiate of this condition from other gynecological diseases (ex. miscarriage, ovarian cyst/tumor torsion, ovary inflammation), urological (ex. bladder inflammation) or gastroenterological (ex. appendicitis). The basis of well conducted diagnoses is detailed interview and physical examination, USG, as well as indication of chorionic gonadotropin level [4]. In case of lack the tangible cause of the patient's complaints, diagnostics should be repeated deferred for a few days.

Among the risk factors for ectopic pregnancy are: past pelvic inflammatory conditions (etiologic factors: chlamydia, gonorrhea, mycoplasma), assisted reproduction (in vitro procedure), patient's age (over 35), nicotine, intrauterine device (IUD), endometriosis, pelvic surgeries [5].

Once an ectopic pregnancy increases the risk of another one by 7,5% and a double by about 10% [6]. The abovementioned factors are responsible for the impairment of movements the fallopian tube and ciliary apparatus. Although in most cases a factor causing an ectopic pregnancy is unknown, but an attempt of identifying is extremely helpful in differential diagnosis.

Ectopic implantation of the embryo may take place within the reproductive organ or beyond him. It's most often located in the tubal tube, which account for 90% of cases, the remaining 10% of locations relate to the cervix, ovary, abdominal cavity and scar after a cesarean section, due to a constant growing percentage of performed cesarean section [7].

Hormonal oral contraception reduces the risk of ectopic pregnancy: using binary tablets. Tablets containing only progestogen carry a greater risk of developing ectopic pregnancy. Intrauterine devices containing copper have a lower risk of implantation an ectopic pregnancy, while those releasing levonorgestrel increases the risk [8].

Pregnancy with an unknown location is a clinical situation in which we get positive pregnancy test results and absence of gestational sac in cavity of uterus during pregnancy transvaginal ultrasound examination. It requires observation and diagnostics to determine final recognition. Serial determination of the HCG β value is helpful, which should be doubled every 48 hours with normal intrauterine pregnancy. Every deviation can help in the differential diagnosis of ectopic pregnancy, early pregnancy miscarriage and biochemical pregnancy. In case of diagnosed ectopic pregnancy, there are several types of therapy: expectant attitude, pharmacological or surgical treatment [9]. Patient with: β HCG concentration in the blood

is low – less than 1000 mIU/ml in diameter of the gestational sac in the fallopian tube area doesn't exceed 4 cm and there is no bleeding from the birth canal and symptoms of fallopian tube rupture as well as the pregnancy itself is diagnosed in early stage may decide on repetitive controls combined with transvaginal USG and concentration assessment of β HCG in serum. This method is used, because a large percentage of ectopic pregnancies is spontaneously absorbed or miscarriage [10]. If the patient's condition does not improve, stable levels of chorionic gonadotropin are maintained or it is building up, a decision of implementing other treatments must be made. The pharmacological method is the administration of methotrexate. The drug is toxic to rapidly dividing cells including developing embryo cells. The recommended dose is 1 mg/kg body weight. In a single dose regimen, there is no need for folic acid supplementation. Then β HCG is determined on 4 and on day 7 after methotrexate intake. No decrease of β HCG by a minimum of 15% on day 7 is an indication for the second dose [11]. Using the described scheme in the patient's stable clinical condition: no lower abdominal pain, no signs of intra-abdominal bleeding and fallopian tube continuity. Contraindications for methotrexate administration are: HCG β concentration above 3500 mIU/ml, diameter of fallopian tube changes above 4 cm and confirmation of embryo's heart function. Side effects

Tab. 1. Workflow

Day 1 – preliminary investigation	<ul style="list-style-type: none"> · β HCG determination in serum, morphology · TVS
Day 3	<ul style="list-style-type: none"> · β HCG determination in serum · TVS · Laboratory parameters determination (morphology, SPAT, ALT, creatinine, blood group) · Methotrexate injection at a dose of 1 mg/kg body weight i.m.
Day 4	<ul style="list-style-type: none"> · β HCG determination in serum · administration of anti-D 50 μg immunoglobulin to women with a negative Rh factor (in accordance with RCOG guidelines no. 22) · further outpatient treatment
Day 7	<ul style="list-style-type: none"> · β HCG determination in serum · TVS · Second dose injection with MTX, if the β HCG level decreases below 25%
Weekly	<ul style="list-style-type: none"> · β HCG determination in serum until it reaches a level below 15 mIU / ml · TVS
At any time regardless of MTX treatment	<ul style="list-style-type: none"> · Surgery in case of patients with acute abdominal symptoms

include: abdominal pain, lack of appetite, nausea, vomiting, difficulties in swallowing, diarrhea, gastrointestinal ulceration, gastrointestinal bleeding, hemorrhagic enteritis, intestinal perforation. The medicine is usually well tolerated by patients, but the most important is strict monitoring of general health [12]. Effectiveness of used pharmacological method is assessed on the basis of the image in transvaginal USG and assessing the dynamics of HCG β changes. Patients who are not eligible for methotrexate or we observe no decrease in chorionic gonadotropin or an increase in its value, surgery treatment remains: laparoscopy or laparotomy.

The study involved 134 patients, diagnosed with ectopic pregnancy of which 126 were located in the fallopian tube, 2 in the cervix, 1 in the cavity peritoneal, 3 in a scar after cesarean section and 2 pregnancies have been reported heterotropic (coexistence of intrauterine and ectopic pregnancy). 39 patients were treated with methotrexate, the remaining 95 were qualified for surgery procedure. Both heterotropic pregnancies were treated laparoscopically, of which in one case intrauterine pregnancy was miscarried, in the second one developed normally and it ended with delivery on time.

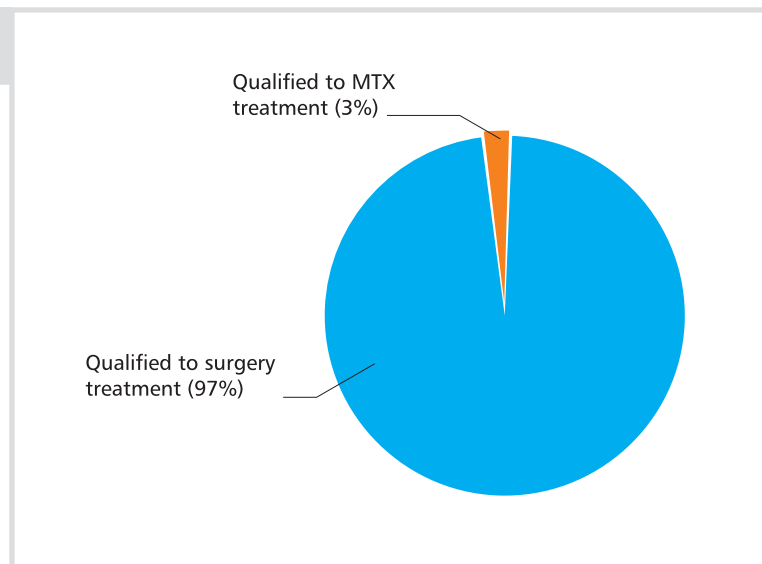
Test description: diagnostics, treatment and protocol with MTX

Ectopic pregnancy was diagnosed directly on the basis of transvaginal ultrasound examination associated with the absence of a gestational sac in uterine cavity, positive β HCG and clinical

signs. Symptoms of the examined patients overlapped with symptoms characteristic of the ectopic pregnancy picture: pain in the lower abdomen, cessation of menstruation, birth canal bleeding. In our diagnostics, we based on a detailed interview (first day of the last menstrual period, identification of the risk factors), physical examination (exclusion of peritoneal symptoms) and gynecological. Connecting with results of serial β HCG determinations and transvaginal USG allowed to early qualification for pharmacological treatment of ectopic pregnancy. It is assumed that with β HCG \geq 1500-2000 mIU/ml ectopic pregnancy should be visible during transvaginal USG. All hemodynamically, stable patients who do not found intrauterine pregnancy were referred to observation. Every 48h β HCG level was measured and there were USG control tests performed. Abnormal increase of β HCG concentration in next 2 days and a visible change within the appendages in an ultrasound examination suggests ectopic pregnancy and it is a direct indication for the pharmacological treatment. The occurrence of any contraindications should be considered and the patient's ability to cooperate should be evaluated (distance from the place of living from hospital) in outpatient observation period.

After termination of MTX treatment, patients were informed about the need of using effective contraception for 6 months, due to an increased risk of miscarriage and fetal malformation.

Fig. 1. Procedures for patients with confirmed ectopic pregnancy



RESULTS

Over 10 years, ectopic pregnancies were diagnosed and treated in 134 patients: 126 cases of fallopian tube pregnancy and 8 cases of ectopic pregnancy with different location than the fallopian tube of which two were heterotopic pregnancies. Analyzing the tubal pregnancies group (126 women): 72% (91 cases) were treated surgically, the remaining 35 patients (28%) were qualified for pharmacological treatment with MTX.

In the patients group qualified for surgery: the dominant procedure was laparoscopy to which 47% patients were qualified which is 59 cases, during 8 laparoscopies there was a conversion to laparotomy which was mainly due

to: heavy bleeding into the peritoneal cavity, obesity and other surgical difficulties. In case of 25% of patients (32 cases), laparotomy was chosen due to indications of life saving.

Patients qualified for pharmacological treatment constituted a group of 39 people: in 31 cases, complete remission was achieved after one dose of MTX, for 8 patients there was need of second dose which help 4 patients with complete remission and remaining 4 patients as a result of ineffective pharmacological treatment were qualified for surgical treatment – laparoscopy. Percentage of patients treated with MTX in proportion to the whole study group is only 28%, but therapeutic success was achieved in this group in 90% of patients.

Fig. 2. Surgical methods in the ectopic pregnancy treatment

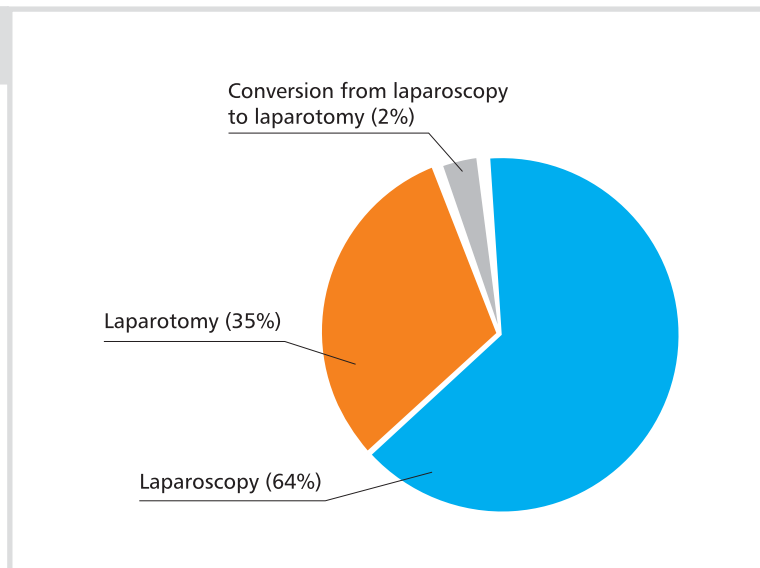
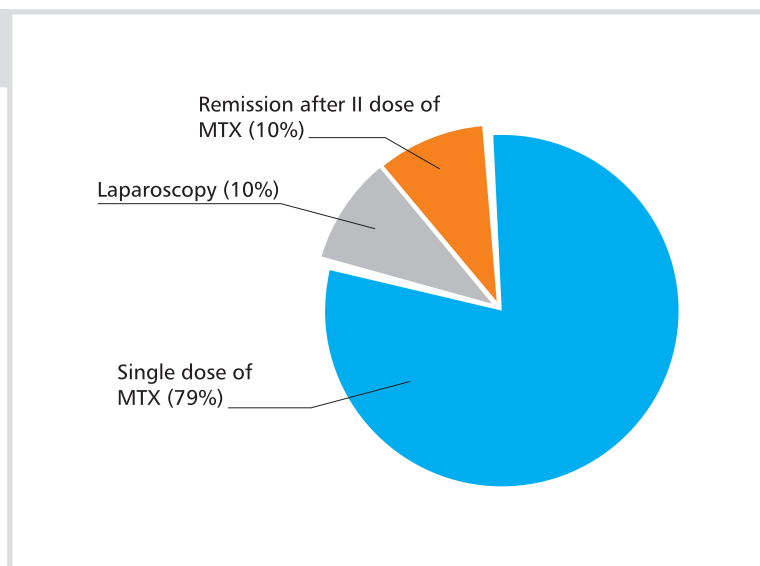


Fig. 3. Pharmacological treatment for patients with ectopic pregnancy



CONCLUSIONS

1. Pharmacological treatment is the first-line healing in the group of early ectopic pregnancies and it can be an effective treatment method allowing to avoid surgery.
2. β HCG level and TVS are qualifying methods the early ectopic pregnancy for MTX treatment.
3. Improving recognition and early qualification to pharmacological treatment increases the chance of successful healing and women's fertility preservation.

1. **Goksedef BP, Kef S, Akca et al.** Risk factors for rupture in tubal ectopic pregnancy: definition of the clinical findings. *Eur J Obstet Gynecol Reprod Biol.* 2011;54(1):96–99.
2. **Khan KS, Wojdyla D, Say L et al.** WHO analysis of causes of maternal death, a systematic review. *Lancet Lond Engl* 2006;367:1066–74, [http://dx.doi.org/10.1016/S0140-6736\(06\)68397-9](http://dx.doi.org/10.1016/S0140-6736(06)68397-9).
3. **Bręborowicz G.** (red.). *Położnictwo i ginekologia*. PZWL 2015:89 ?ISBN 83-200-3082-X?.
4. **Surynt E, Osuch B, Timorek-Lemieszuk A.** Współczesne metody rozpoznania ciąży pozamacicznej. *Ginekologia i Położnictwo Medical Project* 2008;10(4):29-40.
5. **Dart RG, Kaplan B, Varaklis K.** Predictive value of history and physical examinations in patients with suspected ectopic pregnancy. *Ann Emerg Med March.* 1999;33:283-290.
6. **Bręborowicz G** (red.). *Sytuacje kliniczne w położnictwie*. PZWL 2019:71 ISBN 978-83-200-5006-6.
7. **Bouyer J, Coste J, Shojaei T et al.** Risk factors for ectopic pregnancy: a comprehensive analysis based on

- a large case-control, population-based study in France. *Am J Epidemiol.* 2003;157(3):185–194, indexed in Pubmed: 12543617.
8. **Barnhart KT.** Clinical practice. Ectopic pregnancy. *N Engl J Med.* 2009;361(4):379–387, doi:10.1056/NEJMcp0810384, indexed in Pubmed: 19625718.
9. **Surynt E, Osuch B, Timorek-Lemieszuk A.** Współczesne metody leczenia ciąży pozamacicznej. *Ginekologia i Położnictwo Medical Project* 2008;10(4):41-46.
10. **Prevost RR, Stovall TG, Ling FW et al.** Single-dose methotrexate for treatment of ectopic pregnancy. *Obstet Gynecol.* 1991;77(5):754–757. indexed in Pubmed: 2014091.
11. **Barnhart KT, Gosman G, Ashby R, et al.** The medical management of ectopic pregnancy: a meta-analysis comparing “single dose” and “multidose” regimens. *Obstet Gynecol.* 2003;101(4):778–784. indexed in Pubmed: 12681886.
12. **Bręborowicz GH, Dworacka M (red.) Czuczwar P.** *Farmakologia w położnictwie*. PZWL, 2019 ISBN 978-83-200-5600-6.

REFERENCES