Success rate of methotrexate in the conservative treatment of tubal ectopic pregnancies

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Abstract. An ectopic pregnancy (EP) involves the implantation of the gestational sac outside the uterine cavity. In the event of diagnosing an EP, the current medical approach is to avoid surgery and to preserve fertility whenever possible; therefore, methotrexate (MTX)-based therapy has become prominent in recent years. MTX, a drug usually used to treat severe forms of autoimmune diseases and several types of cancer, has proven its utility in the conservative treatment of EPs. The success rate of MTX correlates with lower values of β subunit of human chorionic gonadotropin hormone (β-hCG) serum levels, especially below 2,000 mUI/ml, side effects being insignificant. In the present study, the results obtained concerning the success rate of MTX in the conservative treatment of EPs were obtained at the Department of Obstetrics and Gynecology of the Bucharest University Emergency Hospital from January 2014 to December 2020. The aim of the present study was to highlight the necessity for revising current guidelines for ectopic pregnancy medical treatment in order to manage this pathology optimally and to select carefully the proper treatment, whether medical, surgical or expectant management, so that morbidity is reduced to a minimum.

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Introduction

An ectopic pregnancy (EP) represents the implantation of the gestational sac outside the endometrium of the uterine cavity, and is overall considered a public health problem, judging by the high incidence number reported in recent decades and by its potentially life-threatening medical emergency due to tubal rupture. Previous findings revealed that in the UK the incidence of EP is 11.5 per 1,000 pregnancies and the mortality is 0.4 per 1,000 EP (1): studies from the United States showed the lowest and highest reported incidence, respectively, to be 6.4 and 20.7 per 1,000 EP (2,3). The main risk factors are represented by a previous EP, congenital genital tract anomalies, tumors or history of tubal surgery that distort the normal anatomy, inflammatory pelvic disease, tubal sterilization, combined hormonal contraception or intrauterine device, increasing age, cigarette smoking, assisted reproductive techniques and other medical conditions related to the history and treatment of infertility (4-7). The most common implantation site of an EP is the fallopian tube (96%); other anatomic sites are ovary, abdominal cavity, endocervical canal, hysterotomy scar and the myometrium (8).

As a result of technological progress in high-resolution transvaginal ultrasonography and in the sensitive testing of beta subunit of human chorionic gonadotropin hormone (β-hCG), the EP can be earlier diagnosed, avoiding further complications and improving morbidity and mortality. An early diagnosis of EP allows a more conservative resolution of the pathology. The physician may choose between medical treatment of the EP using methotrexate (MTX), surgical treatment or even expectant management, in selected cases.

The clinical features of EP are represented by a history of amenorrhea, pelvic pain and metrorrhagia (9). An EP may be diagnosed in 90% of cases by systematic transvaginal examination corroborated with β-hCG monitoring (10-15). The ultrasonographic diagnosis of an EP is based on

the visualization outside the uterus of the gestational sac, which contains a yolk sac or embryo with or without cardiac activity (11). The most common finding present in at least 89% of EP cases is represented by a complex inhomogeneous extraovarian adnexal mass; another suggestive ultrasonographic finding is described as a tubal ring which represents an extraovarian adnexal mass incorporating an empty gestational sac (11). There are also findings that only suggest the presence of an EP, but they are not diagnostic. Endometrial thickness can be an indicator of EP; during normal intrauterine pregnancy the ultrasound shows a mean endometrial thickness of 17.2 mm versus a mean of 12.7 mm in EP (15). Douglas and Morrison's pouch should also be inspected for fluid (15). β-hCG produced by the placental syncytiotrophoblast cells is essential for the diagnosis of viable pregnancy (16-18). Intrauterine viable pregnancy is supported by the tendency of β-hCG to double every 48-72 h; a suboptimal increase, below 66%, is highly suggestive for an EP (19). A β-hCG level between 1,000 and 3,500 mUI/ml, and the absence of a gestational sac inside the uterine cavity, highly suggests an EP (16). The differential diagnosis should include miscarriage, implantation bleeding of an intrauterine pregnancy, subchorionic hematoma, gynecologic pathology (ovarian torsion, uterine fibroids, cervical polyps) and gestational trophoblastic disease (19).

When diagnosing a tubal pregnancy (TP), the treatment options depend on the clinical and paraclinical evaluation of the patient, particularly on the hemodynamic status. The treatment options of TP include an expectative approach with monitoring of the β-hCG value trend, MTX therapy administered intramuscularly, intravenously or injected directly into the gestational sac and surgical treatment consisting of salpingostomy or salpingectomy. The current approach is to avoid surgical treatment and to preserve fertility whenever possible. MTX-based therapy has become increasingly popular in recent years for the medical treatment of TP, along with the close monitoring of the β-hCG value dynamics (20,21). MTX therapy is also used in combination with uterine artery embolization or supra-selective embolization of the tubal branches of uterine and ovarian arteries for the treatment of cervical pregnancies or caesarean scar pregnancies, the depth of implantation of the gestational sac being dependent on the location of the EP (21-23).

Because of the life-threatening potential, all cases of diagnosed TP must be evaluated in order to establish the need for emergency surgery (hemodynamically unstable patient and/or suspicion of imminent or ongoing tubal rupture). If the case does not require immediate surgery, the next step is the evaluation of the β-hCG serum level. If the β-hCG serum value is above 5,000 mIU/ml, surgery is preferred. Furthermore, for patients with lower β-hCG serum values it is mandatory to evaluate via ultrasonography the presence or absence of embryonic cardiac activity; if present, surgery is preferred (21,23). MTX therapy may be suggested if the embryonic cardiac activity is absent and if there are no contraindications for such therapy including hypersensitivity to MTX, heterotopic pregnancy, breastfeeding, medical conditions such as immunodeficiency, active pulmonary disease or peptic ulcer, or extensive abnormalities in hematologic, hepatic or renal laboratory tests (24,25). Concerning patients with renal insufficiency, MTX having a renal clearance, one dose could cause severe complications including acute respiratory distress, bone marrow suppression, or bowel ischemia (26,27). Finally, the personal preference of the patient should be considered, as the patient should also be perfectly compliant with close monitoring.

The criteria for expectant management of TP include asymptomatic patients, low serum quantitative β-hCG values (<200 mIU/ml), pelvic ultrasound with no extra uterine mass and no extra uterine gestational sac, compliant patient with the proposed strategy, understanding the risks and clinical significance of an EP, patients wanting to avoid both surgery or MTX therapy and patients prepared to reach a medical unit if clinical conditions worsened (28).

MTX is usually used as a cytostatic, as well as an antineoplastic, immunosuppressive and anti-inflammatory agent, which inhibits cell proliferation and protein synthesis by suppressing the metabolism of purine bases and nucleic acids. Tetrahydrofolic acid is required in the synthesis of purine bases and nucleic acids and it is produced after the reaction between dehydrofolate reductase and folic acid. MTX is a folic acid analogue, which presents a similar structure and acts as an antagonist by binding to dehydrofolate reductase, leading to lower levels of tetrahydrofolic acid. MTX also affects cells with a high rate of division (29). This characteristic is used in the treatment of EP, active rheumatoid arthritis, non-Hodgkin's lymphoma, breast cancer, cutaneous T-cell lymphoma, gestational trophoblastic disease, desmoid tumors and other neoplastic conditions (30-33).

The evaluation and treatment protocol, after the positive diagnosis of a tubal pregnancy, includes several steps: retreatment laboratory testing, ceasing any administration of folic acid supplements, avoidance of non-steroidal anti-inflammatory drug therapy, as well as physical activity and sexual intercourse, repeated pelvic examinations due to possible tubal rupture, and sun exposure to reduce the risk of MTX dermatitis (26). The next step involves selecting the MTX therapy protocol: single dose, two-dose or multiple-dose protocol. Single-dose protocol suggests a single intramuscular dose of MTX, calculated as 50 mg/m^2 of the body surface area (34-37). The β-hCG serum level is measured on day 1, 4 and 7. If the β-hCG level decreases less than 15% between day 4 and 7, a second dose should be administered (25,26,38,39); this occurs in approximately 15-20% of cases. Further monitoring involves weekly β-hCG serum level dosing, until an undetectable level is reached. If the decline of β-hCG values is not favorable, surgery should be performed. Two-dose protocol includes two MTX doses of 50 mg/m^2 offered on day 1 and 4. The β-hCG serum level is tested on day 1 and 7 and should decrease more than 15%; if not, a third dose is administered, followed by retesting on day 11. If the decrease is less than 15%, a fourth dose may be offered, with retesting on day 14. If the decline is again not reassuring, surgery should be performed (39). Multiple-dose protocol involves MTX therapy administered on days 1, 3, 5 and 7 (1 mg/kg per day, intramuscular) combined with 0.1 mg/kg leucovorin on days 2, 4, 6 and 8. In the single-dose protocol, leucovorin is not recommended. The β-hCG level is monitored on days 1, 3, 5 and 7, and this level is expected to decrease more than 15% from the previous testing. After the treatment is finished, the monitoring phase is initiated by weekly β-hCG testing until undetectable.

Thus, the aim of the present study was to highlight the necessity for revising current guidelines for EP medical treatment using MTX, in order to manage this pathology optimally and to select carefully the proper treatment, whether medical, surgical or expectant management, so that morbidity is reduced to a minimum.

Patients and methods

Patients. We conducted a retrospective study, including 61 women aged between 17 and 46 years diagnosed with EP and treated with MTX at the Department of Obstetrics and Gynecology of the Bucharest University Emergency Hospital, during the period, January 2014-December 2020. The cases were analyzed by collecting data from the Medical Statistics Department of the hospital, without inclusion of personal information. The agreement of the ethics committee (no. 17622/10.04.2018) was required and obtained from the University Emergency Hospital of Bucharest without the need of informed consent for study participation of the patient/legal representative in the case of minors. In total, 509 patients diagnosed with EP were analyzed during the mentioned period, extracting from the database, the medically treated patients, who were advocated in two groups: successful medically treated group (42 patients) and unsuccessful medically treated group (19 patients). Conservatory treated patients were analyzed using clinical and hemodynamic parameters, ultrasound evaluation and a β-hCG seriated values trend aiming to identify the actual and practical predictive profile of successful medically treated cases of EP.

The inclusion criteria consisted of pregnant patients without evidence of an intrauterine pregnancy on transvaginal ultrasound, associated with visualization of an extrauterine gestational sac with embryo or yolk sac visible on TVUS, plus MTX administration after informed consent was obtained. The exclusion criteria comprised ruptured ectopic pregnancies exclusively surgically treated, renal, pulmonary and liver disease, immunodeficiency, and concomitant intra- and extra-uterine pregnancies.

Methods. Unit protocol for admitted hemodynamic stable patients suspected of EP based on pelvic pain and/or scant brown metrorrhagia, a routine pregnancy test and a transvaginal ultrasound examination, included: clinical observation and caution for pelvic-abdominal pain, metrorrhagia or faintness, blood pressure and pulse monitoring, β-hCG trend, repeated transvaginal ultrasound, complete blood count, liver and renal tests, blood type and Rh, Human Immunodeficiency and hepatitis B and C virus screening. The patients fulfilling the criteria for medical treatment and requiring MTX administration underwent the single- or multiple-dose protocols with further monitoring of the clinical status, ultrasound evolution and β-hCG seriated values during treatment as well as β-hCG monitoring after the protocol ended until the β-hCG serum level became undetectable. All the patients receiving MTX were informed of the risks involved and signed an informed consent form, in order to receive the medication. Patients with Rh incompatibility received an intramuscular dose of 300 mcg of specific anti-D immunoglobulin. Patients with hemoperitoneum or with decreasing β-hCG serum levels were excluded from the study. Absolute contraindications of MTX treatment were considered: hemodynamic instability, hemoperitoneum, intrauterine pregnancy, hypersensitivity to MTX, severe medullary depression, active pulmonary pathology, peptic ulcer, severe renal pathology, severe liver pathology, or the impossibility of consistent monitoring of β-hCG. Patients with contraindications for MTX therapy and those who left the hospital contrary to medical opinion were excluded from the study. The patients with relative contraindications consisting in β-hCG serum level of over 5,000 mIU/ml, uterine tube diameter ≥3.5 cm, present fetal cardiac activity or an embryo sac larger than 4 cm were accepted for MTX therapy if they refused laparoscopic management as a first line of treatment.

Statistical analysis. The data were collected using Office-Excel version 14.7.7. SPSS 12.0 (IBM Corp.) Pearson's correlation was used for statistical analysis, and the statistical significance threshold was set at $P<0.05$. The characteristics of each group were calculated using 'Descriptive statistics'.

Results

During the selected period, 509 patients were diagnosed with extrauterine pregnancy, including 13 patients who were discharged on request or left the hospital contrary to medical advice from the first day of hospitalization, after a single sampling of β-hCG. Medically treated patients were 61 (11.98%). Patient supervision was performed using repeated dosing of β-hCG serum levels every 48 h and also by using transvaginal ultrasound. The MTX therapy was successful for 42 patients (68.85% of cases) representing group 1 of our study, β-hCG serum levels decreasing during hospitalization (Fig. 1). In 8 cases, a slight increase in the β-hCG value was observed, mainly consisting of several tens of units in the first 48 h after the administration of MTX, which led to its subsequent decrease thereafter. The average period of hospitalization was 9 days, with a minimum of 3 and a maximum of 22 days.

In the second group, including 19 cases of 61 medically treated (31.15%), MTX therapy failed and surgery was necessary, as the β-hCG serum level increased or the patients' symptomatology during hospitalization worsened, in most cases complaining of acute pelvic pain. In 3 cases the patients who received MTX were discharged, but returned 10-15 days later to the emergency ward with hemoperitoneum (Fig. 2): one patient was discharged on demand 48 h after MTX administration, with an insignificant β-hCG decrease, from 1,908 to 1,846 mIU/ml (3.24% decrease), one patient was also discharged on demand after a 48 h increase in β-hCG from 3,682 to 3,738 mIU/ml and another patient was discharged after a decrease in β-hCG from 13,760 to 4,085 mIU/ml (total decrease of 70.3%). From the 19 cases needing surgery, 9 hospitalized patients including the three patients that were discharged and returned with acute pelvic pain and signs of peritoneal irritation, required emergency surgery as the second line of therapy. In patients where MTX therapy failed and hemoperitoneum was detected, marked increasing of the β-hCG serum level was observed during repeated determinations, except for the 2 cases described above (Fig. 2). At the time of hemoperitoneum formation in the other patients, the β-hCG level was at an

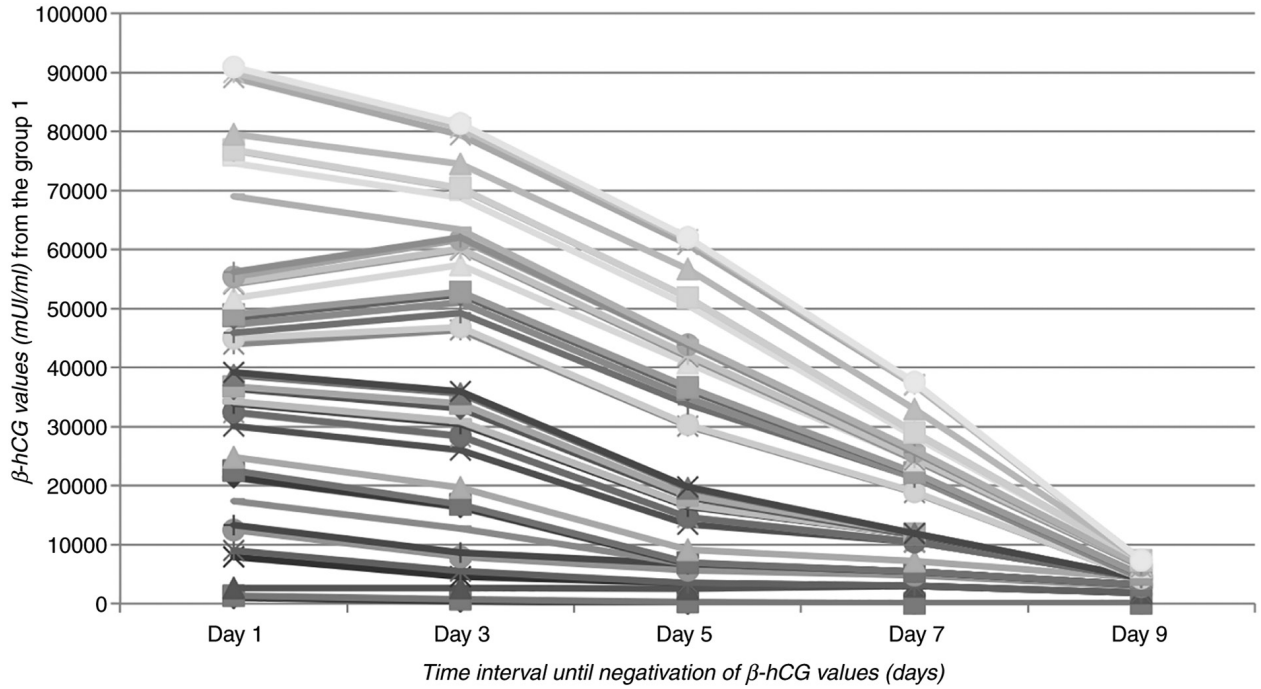

Figure 1. Evolution of β-hCG values (mIU/ml) in each patient from group 1 (n=42), where the conservative approach was successful. Values show a decreasing trend in all cases, even though the decrease is not always linear and an increase was observed prior to the final decline. Each line represents a patient. The x-axis represents time (days). The y-axis represents β-hCG values (mIU/ml). β-hCG, β subunit of human chorionic gonadotropin hormone.

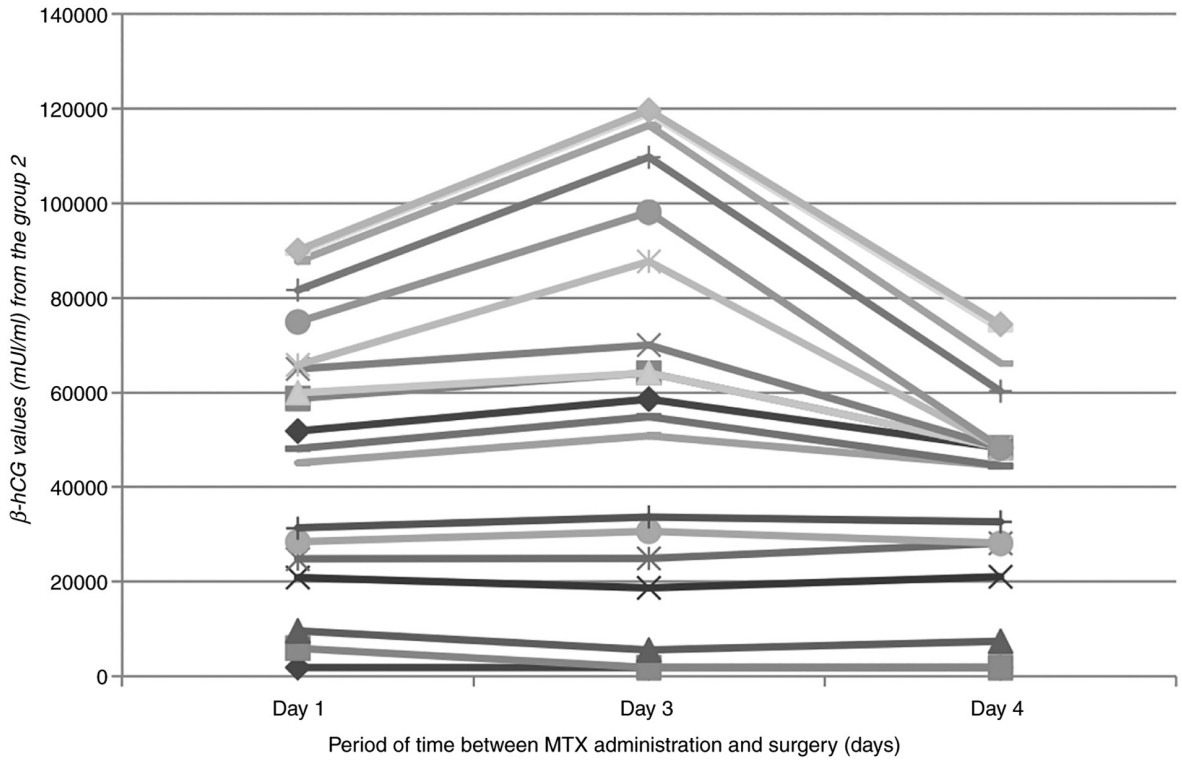

Figure 2. Evolution of β-hCG values (mIU/ml) in each patient from group 2 (n=19), where the conservative approach failed. Most of the values fail to decrease and/or emergency surgery had to be carried out. Each line represents a patient. The x-axis represents time (days). The y-axis represents β-hCG values (mIU/ml). β-hCG, β subunit of human chorionic gonadotropin hormone.

average of 4,238 mIU/ml. In 10 cases, elective surgery was performed, due to the maintenance or increase of the β-hCG value: 8 patients underwent laparoscopic intervention and 2 patients had an exploratory laparotomy performed. In the group of hemodynamically stable patients, an average β-hCG value of 7,083 mIU/ml was detected. Patients with β-hCG values under 2,000 mIU/ml had a success rate of 82.7%, statistically significant correlation between the

initial β-hCG level (mIU/ml) and the group in which the patient was included (P=0.003) (Fig. 1). The failures of medical therapy required emergency surgery (14.75%) and elective surgery (16.39%).

Discussion

There are several studies revealing the success rate of a single dose administration of MTX up to 94%, the administration of a single intramuscular dose being better tolerated by the patient and better assimilated rather than the sequence of administration of smaller, serial doses (34,35,37-40).

The success rate of MTX is lower when embryonic heartbeats are detected, correlating with a higher β-hCG serum level (41). The most important factor regarding the prediction of the MTX therapy success rate represents the initial value of the β-hCG level (42). In our study, patients with values <2,000 mIU/ml showed the best response, with higher values positively correlated with being in-group 2, rather than in-group 1. There was no statistically significant correlation between the age of the patients and the success of the conservative therapy.

In the present study, the failure rate of MTX treatment was 31.15%, with almost equal percentages of patients requiring emergency surgery and elective surgery due to increased β-hCG levels, even when two doses of MTX were administered (difference not statistically significant). The high failure rate compared to other studies was correlated with the β-hCG value measured before starting the treatment, which depended on the time frame of when the patient presented to the hospital. Patients usually presented to the hospital when pelvic pain occurred and required immediate care. MTX therapy was also attempted in patients presenting higher β-hCG values, the success rate being of 50% in patients with β-hCG values above 4,000 mIU/ml at the moment of the healthcare unit admission.

Worldwide, the inpatient hospital treatment of EP has decreased while multiple health care visits for a single EP have increased. Taking into account that after MTX administration, rigorous patient supervision is fundamental, with β-hCG monitoring, clinical and hemodynamic parameters monitoring, and any complaints of abdominal-pelvic pain, Kehr's sign (acute pain in the tip of the shoulder), abnormal uterine bleeding, faintness, nausea, tachycardia and blood pressure decrease should raise the suspicion of intraperitoneal bleeding, we strongly recommend that each country to adapt the management of surveillance of medically treated EP cases upon the real promptitude and performance of its own healthcare system. Due to the lack of specific guidance, low level of medical education of some patients and the deficiencies in informational system of the medical care, inpatient hospital treatment of ectopic pregnancy until the β-hCG value has decreased to under the life-threatening level is optimal.

MTX consistently targets rapidly dividing cells, such as gastrointestinal tract cells, epidermal and hematopoietic cells, which are most commonly affected. The side effects of MTX administration consist of nausea, intestinal transit disorders, fatigue, abdominal pain, pancytopenia, increased risk of infections and dermatitis (43). High elevated serum liver enzymes, chronic liver injury, cirrhosis and portal hypertension may occur when given in high doses. As a result of cellular destruction, an elevated uric acid concentration in patients receiving MTX is expected. Breastfeeding is contraindicated because MTX is distributed in breast milk (33). Due to the hepatotoxic effects, it is imperative to screen for chronic viral hepatitis B and C and to recommend reducing alcohol consumption to a minimum in the immediate period following MTX administration. The patient should be counseled to avoid excessive exposure to sunlight and UV lamps for a period of 4 weeks, as there have been recorded cases of dermatitis. Due to the risk of pancytopenia and the increased risk of infection, we recommend the use of external menstrual pads and the avoidance of intravaginal tampons in case of spotting or vaginal bleeding.

In conclusion, the advantage of using MTX in extrauterine pregnancies consists in surgery avoidance, with the possibility of maintaining fertility and the prevention of long-term complications of surgery such as adhesions that may cause chronic pain and modify the quality of life. Medical management of EP should be considered whenever a patient meets the criteria. The success rate of MTX is correlated with lower initial β-hCG serum levels, especially below 2,000 mIU/ml; MTX therapy efficiency decreases with higher β-hCG serum values. At present, the suggested superior cut-off β-hCG value proposed is 5,000 mIU/ml for the medical treatment of EP in the majority of international guidelines. Given our 50% success rate for ectopic pregnancies with β-hCG values over 4,000 mIU/ml, we recommend revising the actual criteria, thereby decreasing the superior cut-off value for optimal future results. With the introduction of MTX therapy, the need for surgery has been significantly reduced, sparing the unnecessary use of resources, avoiding possible surgical complications, providing comfort to the patients and reducing morbidity caused by the surgery. In addition, medical therapy is less invasive, has a diminished cost and presents a similar intrauterine pregnancy rate for future pregnancies.

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Availability of data and materials

Any additional information concerning the study can be requested from the corresponding author on reasonable request.

Authors' contributions

CG, REB, and BMM conceived the article and wrote the draft of manuscript. CG, DIM and TAG collected, analyzed and interpreted the patient data regarding the methotrexate administration for the treatment of ectopic pregnancy. REB, TAG and BMM performed the literature search and conducted the follow-up of the patients. CAZ and FF performed statistical analysis and study description, making a substantial

contribution to the conception of the work and interpretation of data. CG, REB and DIM revised the manuscript critically for important intellectual content. The authenticity of all the raw data was assessed by CG, FF and DIM. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study was conducted in accordance with the World Medical Association Declaration of Helsinki. The data collected retrospectively did not contain personal information and only the Ethics Committee agreement no. 17622/10.04.2018 of the University Emergency Hospital of Bucharest was required and obtained without the need of informed consent or the consent of the patient/legal representative in the case of minors.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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