ECTOPIC PREGNANCY TREATMENT

RETROSPECTIVE COMPARATIVE ANALYSIS OF METHOTREXATE AND SALPINGOTOMY

Principal supervisor: Dr. Justina Kačerauskiene
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SUMMARY

Author of master thesis: Mirta Amblas Pla

Master thesis: “Ectopic pregnancy treatment”

Supervisor of master thesis: Justina Karčenauskiene, MD

Aim of research: To assess the main factors that can influence ectopic pregnancy (EP) management choice, between methotrexate (MTX) treatment and salpingotomy (ST) procedure.

Objectives of research:
1. To evaluate and compare MTX and ST management options, according patient’s characteristics (Pch) (age, comorbidities, demographics, smoking habits, alcohol and drugs usage).
2. To compare MTX and ST according EP risk factors (RF) (previous ectopic pregnancies, tubal damage, pelvic inflammatory diseases (PID), in vitro fertilizations (IVF), and intrauterine devices (IUD)).
3. To compare MTX and ST according previous fertility issues (FI) (previous infertility, previous spontaneous abortions, and previously treated ectopic pregnancies).

Methodology: This study is a retrospective observational study, in which case histories were reviewed and necessary data was obtained. Patients were divided in two groups according management option: Group 1: patients received MTX intramuscular injection, and Group 2: women underwent ST procedure. Comparison between groups was made to analyse factors influencing management options. Statistical analysis was performed by applying SPSS statistics, version 23.

Study participants: 76 selected nulliparous women treated in Kauno Klinikos between 2010 and 2017, due to tubal EP, either by MTX or ST.

Results: Comparing group 1 and group 2 non-statistical differences according Pch was found (p>0,05). Risk factors also reported no statistical differences (p>0,05). According to previous fertility, no difference in choosing MTX or ST according previous IVF procedure or previous infertility diagnosed.

Reporting EPCh, statistical differences were found. In group 1, 28,9% of the cases were detected with β-hCG initial levels <1000 mIU/mL  (p<0,001), 84,2% reported ectopic gestational sac measuring < 4 cm (p=0,96). In this group only 5,2% were complicated EP (p<0,001) and only 5,2% of cases presented ectopic cardiac activity (p=0,006).
Conclusions: 1. Pch are not factors influencing the treatment option (p>0.05), according EP management. 2. RF are not factors influencing EP management option between MTX and ST (p>0.05). 3. Previous FI do not influence management options (p>0.05). 4. Initial β-hCG level choice (p<0.001) presence of cardiac activity (p=0.006) and complications (p<0.001) are EPCh influencing treatment choice. The decision to choose MTX over ST is made in cases reporting no complications, no ectopic cardiac activity, levels of β-hCG <1000 mIU/mL, and ectopic mass size being < 4cm.
ACKNOWLEDGEMENTS

This research is a part of my 6th year of medical integrated studies in the Lithuanian University of Health Sciences, as a Final Master Thesis. I would like to thank Dr. Justina Kačerauskiene personally for helping, teaching and advising me throughout all of the research work.
CONFLICT OF INTEREST
The author reports no conflicts of interest.

CLEARANCE ISSUED BY ETHICS COMMITTEE
Research of master thesis is approved by ethics committee (no. of permission BEC-MF-159/2018)
ABBREVIATIONS

EP – Ectopic pregnancy
MTX – Methotrexate
ST - Salpingotomy
PCh – Patient’s characteristics
RF – Risk Factors
PID – Pelvic inflammatory disease
IVF – *In vitro* fertilization
IUD – Intrauterine device
FI – Fertility issues
EPch – Ectopic pregnancy characteristics
β-HCG – Beta human chorionic gonadotropin
QoL – Quality of life
IUP – Intrauterine pregnancy
US - Ultrasound
TVUS – Transvaginal ultrasound
DHFR - Dihydrofolate reductase enzyme
DNA - Deoxyribonucleic acid
RNA - Ribonucleic acid
NICE - National Institute for Health and Care Excellence
TTP – Time to pregnancy
LUHS – Lithuanian University of Health Science
SD – Standard Deviation
FHR – Fetal Heart Rate
INTRODUCTION

EP is a common clinical condition found in women at reproductive age, particularly in first trimester of pregnancy. Although EP can be implanted in different locations outside the uterine cavity, the most common location is reported as the fallopian tubes.

Nowadays, maternal mortality due to EP has significantly decreased; but EP still remains in 1-2% of pregnancies worldwide, affecting women’s health and future fertility.

Historically, diagnosis and treatment of this condition has been progressing significantly, from a life-threatening condition with no treatment before the 18th century, to an early diagnosed condition by non-invasive advanced technologies in the 21th century.

Management of EP include expectant, medical and surgical approaches.

Health care professionals offer different management option, considering maternal mortality, fertility outcomes, side effects, contraindications, treatment costs, patient condition, EPCh, patient’s preferences, etc. Currently, controversy still exists about the optimal choice of treatment, according these multiple variables.

This article aims to review the current literature on risk factors, diagnosis, management options of ectopic pregnancy and the individualized treatment according patient features, and to perform a comparative retrospective analysis between MTX and ST treatment options, to evaluate patients’ features, RF, FI and EPCh influencing the choice of treatment.
AIM AND OBJECTIVES OF RESEARCH

Aim: To evaluate the main risk factors and patient’s characteristics that can influence tubal EP treatment, to choose between methotrexate injection and salpingotomy procedure.

Objectives of research:

1. To evaluate and compare the choice of treatment according PCh (age, comorbidities, demographics and toxic habits including smoking, alcohol and drugs).
2. To compare MTX and ST according to the main presented RF of EP (previous EP, tubal surgeries, PID, IVF, IUD).
3. To compare MTX and ST according previous FI (previous infertility, previous spontaneous abortions, and previously treated EP).
4. To compare MTX and ST according EPCh (gestational age, tubal mass size, \(\beta\)-hCG, hemostability and patient condition).
1. LITERATURE REVIEW

1.1. Definition of ectopic pregnancy

EP is an acute abdominal and gynaecological condition, found in women at reproductive age, which occurs when the developing blastocyst gets implanted outside the uterine cavity [1]. This condition can compromise women’s health and future fertility [9].

Nowadays improvements in diagnostic methods allow a more accurate and early diagnosis of this condition, and a subsequent early management. This early management of EP offers treatment options according to the patient’s characteristics, considering not only the survival, but also the quality of life (QOL) during treatment and fertility outcomes [5, 21].

The best approach should be decided according to patient’s medical status, however, many variables can influence it, variables such as success rates, complications, side effects, treatment costs, and subsequent fertility outcomes [12]. Also, taking into account the patient’s preferences [23].

Preservation of the patient’s fertility is the currently discussed issue in EP management, mainly after laparoscopic ST and MTX injection [7, 9].

1.2 Classification of ectopic pregnancy according anatomical locations

The majority of EP, 98%, occur in the fallopian tubes. Being the ampulla the most common tubal part of EP attachment. Other tubal EP attachment sites include: isthmus, infundibulum and fimbria [2, 8]. Extratubal pregnancies are those in which the blastocyst is implanted in the ovaries, endocervical canal, peritoneal surfaces or abdominal viscera, respectively named as ovarian, cervical and abdominal pregnancies. Uterine EP cases, which are proportionally lower than other types of EP, include attachment to cesarean scars, and entire or partial attachment to the myometrium [1].

1.3 Risk factors for ectopic pregnancy

It is well known that several RF influence in developing extra uterine implantations [21]. Potential RF include previous EP, history of tubal damage or tubal surgery, history of PID, usage of IUD, assisted reproduction technology techniques like IVF, and smoking habits [7]. The assessment of RF can help to identify high risk women, in which close monitoring would be very beneficial to provide an early diagnosis of EP [7].

1.4 Clinical picture of ectopic pregnancy

An embryo, to develop normally, needs to be implanted in the endometrium. When the embryo is implanted elsewhere is unable to develop in normal conditions.

In EP condition bleeding from the implanted location can occur, and, in some cases, even
rupture [2]. Therefore, EP condition should be considered in any women at reproductive age, with or without abdominal pain, together with abnormal vaginal bleeding [7].

Traditionally, the most common clinical findings were: lower abdominal pain, vaginal bleeding and amenorrhea, symptoms forming the classical triad [2]. This triad, was firstly described by an Italian anatomist Giovanni Domenico-Santorini (1681-1737), but nowadays is only present in 50% of ectopic pregnancies, being a poor accurate diagnostic finding [21].

EP can present different clinical pictures, from asymptomatic conditions to complicated EP presenting shoulder pain, peritonitis, severe pain, severe hemorrhage or signs of shock. Other clinical symptoms include nausea, vomit, breast tenderness, symptoms that mimic intrauterine pregnancy (IUP), or any of the symptoms from the classical triad [2,13].

Clinical signs such as cervical motion tenderness, palpable adnexal mass and adnexal tenderness are examination findings that increase the likeliness of EP.

Due to no single pathognomic sign or symptom, history, RF and examination are important factors in EP, but insufficient to perform a diagnosis. The diagnosis is achieved by a combination of clinical presentation and complementary tests [21]. Also, clinical pictures can be useful to evaluate the presence of fallopian tube rupture [13].

1.5 Diagnosis of ectopic pregnancy

According literature, EP is a condition increasing in incidence in developed countries, but fortunately new diagnostic methods allow an early diagnosis [5], reducing the risk of tubal rupture and increasing medical management success [7]. Currently, EP diagnosis prioritizes ectopic mass identification outside uterus, over the identification of IUP absence [21].

EP diagnosis is based on ultrasonography examination and β-hCG levels [7]. Findings like ectopic cardiac activity or ultrasound (US) detection of an embryo outside uterus are absolute criteria for diagnosis [2]. Findings in abdominal US suggesting EP, but being inconclusive, include: absence of intrauterine sac, presence of ectopic mass and identification of fluid in the Douglas pouch. To confirm EP in inconclusive US findings, β-hCG in serum is assessed [7].

Due to abdominal US limitations, in early cases, transvaginal ultrasound (TVUS) is the most useful technique [7]. Interpretation of TVUS findings should be correlated to gestational age and β-hCG level, being a visible gestational sac at 5.5-6 weeks of gestation and above 1,500 mIU/mL hormone levels [7].

In unclear diagnoses, 48 hours serial serum β-hCG is measured, which allow us to distinguish between a failing pregnancy and active pregnancy.

However, a β-hCG level does not distinguish location of pregnancy (IUP or EP). After 48 hours of the β-hCG levels being monitored, levels doubling or increasing around 66%, suggest a healthy
IUP. Even in 15% of healthy intrauterine pregnancies levels do not rise by 66%. And, even in some cases, 13% of ectopic pregnancies, levels can rise around 66%.

Therefore, in early stages, diagnosis of EP is based on TVUS not showing IUP, with presence or absence of ectopic mass, and monitored β-hCG levels above the discriminatory zone (>1,500 mIU/mL β-hCG levels). Together with anamnesis, clinical pictures and RF assessments [7].

1.6 Choice of ectopic pregnancy treatment option

Management options for EP include expectant, medical treatment, conservative surgical treatment and radical surgical treatment [5].

To choose treatment modality many factors are considered, including patient age, tubal condition, serum β-hCG levels and the patient’s future fertility desires [6]. Together with factors including success rates, complications, side effects, costs of treatments, surgeon experience, patient condition and fertility outcomes [12].

The choice of treatment, depends on the accurate triage of the patient. Patient categorization has been made by the evaluation of patient according Fernandez score (scoring system of 6 criteria including gestational age, β-hCG, progesterone level, abdominal pain, haemoperitoneum volume and haematosalpinx diameter) or according “level of activity”, concept remaining subject of debate. Considering an active EP an extratubal pregnancy with hemodynamic failure, abundant hemoperitoneum, symptoms of rupture or high β-hCG hormone levels [3].

1.6.1 Expectant management

Expectant managements consist in monitoring serum β-hCG levels until spontaneous recovery occurs. β-hCG levels are assessed every second day initially, and then weekly, to detect a persistent trophoblast [3]. This treatment option is applied to clinically stable women, who presented uncomplicated EP with initial β-hCG measurements less than 1,500 mIU/mL [17].

Expectant treatment is considered safe in women that had been adequately counselled, compliant to treatment pathway with no barriers to healthcare access [21].

The METEX trial showed no differences between expectant management and MTX group in women with far fewer active EP (the criteria just mentioned above), therefore, METEX recommends expectant management as the first line for less active EP, and a MTX as second-line of treatment [3].

1.6.2 Medical treatment

MTX is an antimetabolite drug that acts on actively-proliferating cells, including trophoblastic cells [3]. It inhibits the enzyme dihydrofolate reductase (DHFR), enzyme that reduce folic acid to tetrahydrofolate. This inhibition of DHFR cause a depletion of cofactors required for deoxyribonucleic
acid (DNA) and ribonucleic acid (RNA) synthesis [7].

As any chemotherapy agent acts on rapidly-dividing cells, damaging DNA and causing the inability to divide, causing cell death. Meaning that methotrexate not only affects the blastocyst implanted in the tubes; it also affects rapidly dividing cells of the body, which are in the gastrointestinal tract, hair, skin, nails, bone marrow, ovarian and endometrial cells [3].

MTX is most often administered as a single-dose intramuscular injection, according to the single-dose protocol: a single dose (50mg/m2 or 1mg/kg) is administered on day 0, if β-hCG levels do not drop 15% between day 4 and day 7, a second dose can be administered on day 7 [3].

According to literature, predictors of successful treatment include: Initial β-hCG < 1,000 mIU/mL, absence of gestational sac and no ectopic fetal cardiac activity [17]. However, hormonal level cut-offs ranges from 1,000 to 5000 mIU/mL [22].

A recent study about predictive factors of MTX treatment, a comparison of 400 cases, concluded that pre-treatment β-hCG level is an important factor predicting MTX treatment success, being effective at hormone less than 1,000 mIU/mL, in patients with Fernandez score less than 13 [22]. After treatment initiation, showing small increase or a decrease of β-hCG measurements are also predictors of successful treatment [17].

Therefore characteristics such as adnexal fetal cardiac activity, presence of free peritoneal blood, the size of gestational mass being > 4cm, high initial β-hCG levels >5000 mIU/mL, rapidly increasing β-hCG concentrations (>50%/48h), and β-hCG levels rising continuously during MTX treatment, are predictors of MTX treatment failure [7].

Before any MTX treatment, contraindications are evaluated, including conditions like hepatic dysfunction, renal dysfunction, active peptic ulcer disease, severe anemia, active pulmonary disease, and hemodynamically unstable or immunodeficient patient (Table 1) [7].

Confirmation of no viable IUP must be clear, because in case of viable pregnancy misdiagnosed, MTXe can induce embryopathy, a serious and avoidable complication [21]. The adverse effects of the treatment are most frequently haematological, digestive, hepatic, pulmonary or buccal [22].

According to toxicology literature, this chemotherapeutic agent is fully excreted from the body within a period of 4-6 months after administration [4].

The National Institute for Health and Care Excellence (NICE) recommends MTX treatment as the first-line treatment, for patients able to return for follow-ups, in which US confirmed no IUP, with no significant pain, no ruptured EP, no fetal heartbeat, presenting β-hCG serum levels between 1,500 mIU/mL and ectopic mass smaller than 35 mm [17].

MTX can be administered as post-operative treatment, showing a decrease in failure rate, being beneficial in risk of persistent EP [3].
Post-operative MTX is injected during the first 24 hours after surgery, and it is mainly used in early stage EP, meaning those measuring less than 2 cm, presenting high initial β-hCG levels or in cases of incomplete resection [7].

Table 1. Contraindications to Methotrexate

<table>
<thead>
<tr>
<th>Absolute contraindications</th>
<th>Relative contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>_ Intrauterine pregnancy</td>
<td>_ Embryonic cardiac activity detected by transvaginal ultrasonography</td>
</tr>
<tr>
<td>_ Evidence of immunodeficiency</td>
<td>_ High initial β-hCG concentration (&gt;5,000 mIU/mL)</td>
</tr>
<tr>
<td>_ Moderate to severe anemia, leukopenia, or thrombocytopenia</td>
<td>_ Ectopic pregnancy &gt;4 cm in size as imaged by transvaginal ultrasonography</td>
</tr>
<tr>
<td>_ Sensitivity to MTX</td>
<td>_ Refusal to accept blood transfusion</td>
</tr>
<tr>
<td>_ Active pulmonary disease</td>
<td>_ Inability to participate in follow-up</td>
</tr>
<tr>
<td>_ Active peptic ulcer disease</td>
<td></td>
</tr>
<tr>
<td>_ Clinically important hepatic dysfunction</td>
<td></td>
</tr>
<tr>
<td>_ Clinically important renal dysfunction</td>
<td></td>
</tr>
<tr>
<td>_ Breastfeeding</td>
<td></td>
</tr>
<tr>
<td>_ Ruptured ectopic pregnancy</td>
<td></td>
</tr>
<tr>
<td>_ Hemodynamically unstable patient</td>
<td></td>
</tr>
</tbody>
</table>

1.6.3 Surgical treatment

Tubal EP patients can be treated surgically, either by ST, in which the affected fallopian tube is preserved, or salpingectomy, removal of fallopian tube together with EP [3, 10].

Laparotomy with salpingectomy was the standard procedure until 1978, when laparoscopic ST was first reported [3]. Comparing laparoscopy and laparotomy approaches, laparoscopy allows a faster recovery for the patient and less painful postoperative, providing diagnostic methods and treatment methods, at the same time. In clinical practice the choice depends on the patient and surgeon, factors connected to the EP and preferences [11, 14].

Literature review showed preference of ST over salpingectomy, in patients presenting a healthy contralateral tube [17], and salpingectomy was the preferred treatment option for patients with severe tubal damage or uncontrolled bleeding from tubes [3].

Salpingectomy should be applied to woman with a history of previous EP, history of previous PID, contralateral tubal damage or previous abdominal surgeries [3].

Emergency surgery is indicated in hemodynamically unstable patients or ongoing tubal rupture. In hemodynamically stable patients, surgery intervention should only be performed in patients with a clearly visible mass or ectopic sac in US. In patients presenting contraindications, failed MTX therapy, or heterotopic pregnancy with a viable IUP, surgical treatment should also be considered [3].
Costs of surgery are higher over medical costs, because methotrexate is able to be administered in an office-setting, without need for hospitalization. However in cases presenting predictors of MTX failure, surgery is preferred [11].

1.7 The subsequent fertility after ectopic pregnancy treatment

Fertility is defined as the spontaneous occurrence of IUP [5]. The effect of subsequent fertility is an important fact to consider when choosing the treatment option for ectopic pregnancy, therefore one of the main goals of EP management is the preservation of future fertility, mainly at developed countries [3].

Even management option has an important role in subsequent fertility preservation, other aspects are involved, such as patient’s age, size of ectopic pregnancy, level of serum β-hCG and contralateral patency [6, 12, 15].

MTX causes toxic effects to ovaries, however, this negative effect to fertility is limited to 180 days, after which the effect is reversed [4].

The effect of salpingectomy, removal of the tube, impairs fertility, which is only is preserved by the resting fallopian tube. ST can cause tubal blockage, due to inflammatory factors released and scarring tissue formed. In some cases, tube adhesions and hydrosalpinx are presented after the procedure. Tubal blockage leads to future oocytes not being able to leave fallopian tubes, therefore fertility is impaired [6].

A prospective study from ectopic pregnancies in France, Auvergne registry, evaluated the fertility outcome after EP by assessing the time to get pregnant (time to pregnancy (TTP)), time in which couple achieved to conceive an IUP, in the interval of 2 years after treatment. This study reported similar fertility outcomes after MTX comparing to conservative surgical treatment, and a worse fertility outcome after radical surgery procedures [5]. Another important study to mention is DEMETER study [5], reported similar conclusions from Auvergne registry, that showed no differences between ST and salpingectomy in a period of 2-years after the surgery in active EP and in less active EP [5].

A similar study called ESEP study [10], a controlled trial comparing ST and salpingectomy surgeries in EP, in which women with contralateral tube diseases were excluded, concluded that salpingectomy should be preferred over ST, according the higher recurrent EP results after ST. Being important to mention patients’ strong preference towards salpingectomy, they preferred a complete tubal removal rather than a possibility of EP recurrence [10]. Opposite conclusions reported by DEMETER study, showing higher recurrences of EP after salpingectomy. However both recurrent findings were considered non-significant due to small samples.
2. RESEARCH METHODOLOGY AND METHODS

Research planning: Initially, hypothesis and methodology were designed, new updated literature about ectopic pregnancy was reviewed, and the permissions were collected.

The study focused on factors influencing the choice between treatment options, comparing patients treated with methotrexate against patients treated by salpingotomy procedure. Data from case histories was collected and statistically analyzed, to perform the results and conclusion. And finally the master thesis was written.

The object of study: Factors influencing ectopic pregnancy treatment choice, in seventy-six patients, who presented tubal ectopic pregnancy and were treated with methotrexate or salpingotomy between 2010 and 2017 at the Hospital of Lithuanian University of Health Sciences (LUHS) Kauno Klinikos, in Kaunas, excluding from the research, women with previous children.

Participant selection (population, sample): Seventy-six patients diagnosed with tubal ectopic pregnancy and successfully treated. The same number of patients was collected for each treatment option, two groups were formed:

- Group 1: Patients treated with MTX injection.
- Group 2: Patients treated surgically, by ST procedure

Research methods: This research was an observational retrospective case study.

Methods of data analysis: The analysis was performed by using “SPSS statistics, version 23”. MTX, treatment used in patients from group 1, and ST, management option used in patients from group 2, were compared according to different variables; frequencies and percentatges were calculated.

Demographics characteristics were analyzed such as living place, marital status, alcohol, smoking and drugs intake, and patient comorbidities including epilepsy, anemia, cardiovascular diseases, bronchitis and hepatitis.

RF were evaluated and compared: previous EP, previous gynecological or abdominal surgeries, smoking, PID, endometriosis, and infertility treatment.

And finally, characteristics of EP were assessed including gestational age, intial β-hCG levels, ectopic gestational sac diameter and complications like hemoperitoneum, tubal abortion, tubal adhesions rupture and hemorrhage causing secondary anemia.

SPSS statistics was used to assess the relationship between variables and treatment options; p was calculated by Fisher’s exact test that gives a more accurate value for small samples sizes.
3. RESULTS
During research time, from all the patients treated with MTX or ST between 2010 and 2017 at the Kauno Klinikos, due to tubal EP, 76 were admitted in our study: 38 were admitted to group 1 and 38 were admitted to group 2.

Sociodemographics and patient’s characteristics
Comparative patient’s characteristics and sociodemographic data are shown in Table 2.

**Table. 2. Comparative table of patient’s characteristics and sociodemographic data**

<table>
<thead>
<tr>
<th></th>
<th>Group 1 - MTX</th>
<th>Group 2 - ST</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30 years</td>
<td>16 (42,1%)</td>
<td>15 (39,5%)</td>
<td>0,600</td>
</tr>
<tr>
<td>&gt;30 years</td>
<td>22 (57,9%)</td>
<td>23 (60,5%)</td>
<td></td>
</tr>
<tr>
<td>Marital Status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>16 (42,1%)</td>
<td>18 (47,4%)</td>
<td>0,120</td>
</tr>
<tr>
<td>Married</td>
<td>26 (68,4%)</td>
<td>20 (52,6%)</td>
<td></td>
</tr>
<tr>
<td>Living</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Country</td>
<td>14 (36,8%)</td>
<td>9 (23,7%)</td>
<td>0,159</td>
</tr>
<tr>
<td>City</td>
<td>24 (63,2%)</td>
<td>29 (76,3%)</td>
<td></td>
</tr>
<tr>
<td>Toxic habits</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>1 (2,6%)</td>
<td>0</td>
<td>0,500</td>
</tr>
<tr>
<td>Smoking</td>
<td>14 (36,8%)</td>
<td>9 (23,7%)</td>
<td>0,159</td>
</tr>
<tr>
<td>Drugs</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>5 (13,2%)</td>
<td>6 (15,8%)</td>
<td>0,500</td>
</tr>
<tr>
<td>Medication</td>
<td>5 (13,2%)</td>
<td>5 (13,2%)</td>
<td>0,693</td>
</tr>
<tr>
<td>Allergies</td>
<td>1 (2,6%)</td>
<td>3 (7,9%)</td>
<td>0,370</td>
</tr>
</tbody>
</table>

Comparing marital status of group 1 and group 2, no statistical difference found (p>0,05),
The variable of living location, is not detected statistically significant according EP management option (p>0,05).
In relation to toxic habits, only one patient reported alcohol intake, patient included in group 1. No patients reported drug intake. Non-significant differences were found comparing smoking habits in both groups (p>0.05).

Only a few patients from our study presented comorbidities. There was no statistical difference between group 1 and group 2 (p>0.05). The same number of patients taking medication during EP diagnosis were treated medically and surgically, no differences between management options were found.

Comparing allergies in both groups, no statistical difference (p>0.05) was calculated due to insufficient sample.

The range of age of our selected patients at the time of tubal EP management was from a minimum age of 19 years, to a maximum age of 45 years. Analysing the variable of patient’s age results showed no preference of management options. Fisher-’s exact test was calculated, being p>0.05 meaning no statistical difference regarding patient’s age.

**Risk factors of Ectopic pregnancy**

Table 3 represents the collected and analysed information related to patients’ RF.

From a total of sixteen patients with previous EP, two women had two previous EP, both of them from group 2 (treated surgically), previously, they were also treated surgically (Scheme 1).

Scheme 1 shows women with previous EP, what treatments they receive and in which order. Being surgery the first option in most of the cases, and MTX the option used after EP recurrence.

Women presenting only one previous case of EP, were more commonly treated by MTX rather than being treated by tubotomy procedure, but according Fisher’s exact test calculation (p>0.05) the difference was not statistically significant.

From a total of seventy-six pateints, thirty pateints had previous abdominal surgeries, being the most common appendectomy and ginecological surgeries. From them, seventeen patients presented tubal surgeries, including tubectomies and tubotomies.

Comparing the number of patients treated medically and surgically, more cases of EP patients presenting previous tubal surgeries were treated with MTX injection. However, no dependence between management option and previous surgeries was determined (p>0.05).
### Table 3. Comparative table of risk factors and fertility issues

<table>
<thead>
<tr>
<th></th>
<th>Group 1 - MTX</th>
<th>Group 2 - ST</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous EP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• 1 previous EP</td>
<td>10 (26,3%)</td>
<td>4 (10,5%)</td>
<td>0,200</td>
</tr>
<tr>
<td>• 2 previous EP</td>
<td>0</td>
<td>2 (5,3%)</td>
<td></td>
</tr>
<tr>
<td>Previous tubal surgeries</td>
<td>12 (31,6%)</td>
<td>5 (13,2%)</td>
<td>0,120</td>
</tr>
<tr>
<td>PID</td>
<td>2 (5,3%)</td>
<td>3 (7,9%)</td>
<td>0,500</td>
</tr>
<tr>
<td>Infertility</td>
<td>6 (15,8%)</td>
<td>2 (5,7%)</td>
<td>0,124</td>
</tr>
<tr>
<td>Infertility treatment (IVF)</td>
<td>2 (5,2%)</td>
<td>2 (5,7%)</td>
<td>0,623</td>
</tr>
<tr>
<td>IUD</td>
<td>1 (2,6%)</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Endometriosis</td>
<td>3 (7,9%)</td>
<td>4 (10,5%)</td>
<td>0,500</td>
</tr>
<tr>
<td>Previous abortions</td>
<td>5 (13,2%)</td>
<td>3 (7,9%)</td>
<td>0,124</td>
</tr>
</tbody>
</table>

### Scheme 1. Previous EP treatments

- **16 women**
  - **2 previous EP (2 patients)**
    - 1st EP – tubotomy
    - 2nd EP – tubectomy
    - 3rd EP - tubotomy
  - **1 previous EP (14 patients)**
    - 1st EP –
      - 3 patients – expecting management
      - 5 patients – tubotomy
      - 6 patients – tubectomy
    - 2nd EP
      - 10 patients – MTX
      - 4 patients - tubotomy
In our study few patients presented PID, no differences were found between treatment options (p>0,05).

According endometriosis, there was no statistical difference comparing both treatment options (p>0,05).

And the same result according previous abortions, calculated p>0,05 meaning no statistical difference comparing MTX and ST procedures.

**Fertility Issues**

According patients’ previous fertility, eight patients reported infertility. In women with previous infertility, more cases were treated by MTX compared to ST, data seen in Table 3. This difference was not statistically significant options (p>0,05).

From eight infertile patients, only half of them received treatment by invitro fertilization (IVF) procedure. The exact number of patients with infertility treatment was reported in each management option group. No difference in choosing MTX or ST according previous IVF procedure.

Four patients reported the usage of contraceptive methods at the time of EP diagnosis, however only one patient, from group 1, using an IUD.

**Ectopic pregnancy characteristics**

Table 4, shows comparative data of EP characteristics including clinical picture, gestational age, initial β-hCG levels, size of ectopic mass and complications.

According clinical picture, most of the patients consulted in Kauno Klinikos due to amenorrhea or positive pregnancy test, however, some patients presented vaginal bleeding and abdominal pain. But, only twenty-three patients reported the clinical triad (vaginal bleeding, abdominal pain and amenorrhea).

Patients presented other clinical symptoms and signs, such as abdominal tenderness, nausea, vomit, weakness, adnexal mass, and shoulder pain.

More cases presenting vaginal bleeding were treated by ST, compared to those cases treated by MTX. Similar results, in patients showing abdominal pain. Also from all the patients presenting clinical triad, more cases were treated surgically. On the other hand, in EP only reporting amenorrhea, similar numbers treated by MTX and ST, even a slight increase in number of patients treated with MTX injection.

Comparing the choice of management according to the clinical picture, showed no statistically significant results (p>0,05).
### Table. 4. Baseline characteristics of ectopic pregnancy

<table>
<thead>
<tr>
<th></th>
<th>Group 1 – MTX</th>
<th>Group 2 - ST</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical picture</strong></td>
<td></td>
<td></td>
<td>0,159</td>
</tr>
<tr>
<td>Triad</td>
<td>10 (26,3%)</td>
<td>13 (34,2%)</td>
<td></td>
</tr>
<tr>
<td>Vaginal bleeding</td>
<td>14 (36,8%)</td>
<td>17 (44,7%)</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>22 (57,9%)</td>
<td>25 (65,8%)</td>
<td></td>
</tr>
<tr>
<td>Amenorrhea</td>
<td>30 (78,9%)</td>
<td>29 (76,3%)</td>
<td></td>
</tr>
<tr>
<td><strong>Gestational age</strong></td>
<td></td>
<td></td>
<td>0,644</td>
</tr>
<tr>
<td>&lt;6 weeks</td>
<td>11 (28,9%)</td>
<td>10 (26,3%)</td>
<td></td>
</tr>
<tr>
<td>6-7 weeks</td>
<td>14 (36,8%)</td>
<td>11 (28,9%)</td>
<td></td>
</tr>
<tr>
<td>&gt;7 weeks</td>
<td>13 (34,2%)</td>
<td>17 (44,7%)</td>
<td></td>
</tr>
<tr>
<td><strong>Initial β-hCG levels</strong></td>
<td></td>
<td></td>
<td>0,000</td>
</tr>
<tr>
<td>&lt;1000</td>
<td>11 (28,9%)</td>
<td>5 (13,2%)</td>
<td></td>
</tr>
<tr>
<td>1000-5000</td>
<td>26 (68,4%)</td>
<td>17 (44,7%)</td>
<td></td>
</tr>
<tr>
<td>&gt;5000</td>
<td>1 (2,6%)</td>
<td>16 (42,1%)</td>
<td></td>
</tr>
<tr>
<td><strong>Gestational sac diameter</strong></td>
<td></td>
<td></td>
<td>0,096</td>
</tr>
<tr>
<td>&lt;4 cm</td>
<td>32 (84,2%)</td>
<td>24 (63,2%)</td>
<td></td>
</tr>
<tr>
<td>&gt;4cm</td>
<td>6 (15,7%)</td>
<td>11 (28,9%)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>3 (7,9%)</td>
<td></td>
</tr>
<tr>
<td><strong>FHR</strong></td>
<td>2 (5,3%)</td>
<td>11 (28,9%)</td>
<td>0,006</td>
</tr>
<tr>
<td><strong>Complications</strong></td>
<td>2 (5,3%)</td>
<td>17 (44,7%)</td>
<td>0,000</td>
</tr>
</tbody>
</table>

Gestational ectopic sac diameter was evaluated by US, as part of the EP diagnosis. In patients presenting an ectopic mass measuring <4cm, a higher number of patients from group 1 compared to the number of cases treated surgically. Opposite situation in patients with EP measuring more than 4 cm, in which more cases were treated surgically rather than medically. Three patients had no data about mass size (3,9%), all of them treated by tubotomy procedure. No statistically significant difference was found, when comparing MTX and ST managements (p>0,05).

According the gestational age (ranged 4-15 weeks), no statistically significant differences were seen comparing MTX and ST groups (p>0,05).
Fetal heart rate (FHR), meaning detection of hearth activity of ectopic pregnancy, was found in few cases, two patients from group 1 and eleven patients from group 2.

With regard to the comparison within the groups, there was a statistically significant difference regarding EP management, the calculated p< 0.05. Most of the patients presenting fetal cardiac activity were treated by tubotomu procedure.

Observing initial β-hCG levels results shown in Table 4, reported initial levels <1000 mIU/mL are associated to MTX treatment choice, while β-hCG initial levels >5000 mIU/mL are associated to ST procedure.

While only five patients were treated surgically presenting β-hCG levels <1000 mIU/mL, seventeen patients were treated by ST showing β-hCG levels between 1000-5000 mIU/mL levels.

Statistically significant results were seen comparing both treatment according initial β-hCG levels, calculated p<0.05.

Nineteen cases reported complications of EP. The most common complications being hemoperitoneum, tubal abortion, tubal adhesions rupture and hemorrhage causing secondary anemia. Statistically significant difference was seen comparing both treatments according presence of complications. P-value <0.05, calculated by Fisher’s exact test. In complicated EP, surgical treatment is preferred over MTX management.

In our study only two patients presenting complications were treated by MTX. They presented no ectopic cardiac activity, ectopic sac measuring <4 cm and initial β-hCG levels <1000 mIU/mL.
4. DISCUSSION OF THE RESULTS

EP is a common problem among women at reproductive age. According to the literature, many factors influence management option of tubal EP. In our study we analyzed seventy-six patients, to assess which factors were most influential to management choice, between methotrexate and salpingectomy, in EP condition.

Treatment choices according to patient future fertility is an emergent debate nowadays, and the effect of different management strategies on subsequent fertility is still controversial. However in our study there was no possibility to assess subsequent fertility due to confidential limitations. In fact the rest of the factors were evaluated and analyzed.

In our study, sociodemographic characteristics and EP RF were not influencing EP management choice.

From patients who reported previous tubal surgeries, including tubotomy and tubectomy, a preference of medical management over surgery was seen in our study. Similar findings were found on the article [11], resporting that for women with a prior history of fertility-reducing factors, the preservation of the affected tube produced the largest benefit regarding future IUP. However, in our study even though these findings were seen, this findings were not able to be concluded because the dependence of these variables were not established (p > 0,05).

In our study, in group 1, patients treated by MTX, were often detected $\beta$-hCG initial levels $<1000$ mIU/mL ($p<0,001$), ectopic gestational sac measuring less than 4 cm ($p=0,96$), absence of fetal heart rate ($p=0,006$) and no complications ($p<0,001$).

Compared to group 2, who presented opposite results.

Similar results were found in previous studies, who defined initial $\beta$-hCG less than 1,000 mIU/mL, absence of gestational sac and no ectopic fetal cardiac activity [17] predictors of successful MTX treatment.

In previous studies, cut-off levels ranges from 1,000 to 5000 mIU/mL [22]. In our study $\beta$-hCG levels between 1,000 and 5000 mIU/mL, twenty-six cases were treated by MTX against seventeen cases treated by ST. A preference on MTX over ST was found, in those patients presenting no complications, no ectopic cardiac activity and ectopic gestational sac measuring less than 4 cm.
Therefore we can conclude that in cases which $\beta$-hCG is between 1,000 and 5000 mIU/mL, the next sign to rely is the absence of complications ($p < 0.001$), the next most reliable sign is on the absence of cardiac activity ($p=0.006$), then ectopic mass size being < 4cm ($p=0.96$).
5. CONCLUSIONS

1. PCh such as age, comorbidities, marital status, alcohol, smoking and drugs intake, are not statistically significant difference, in comparison between MTX and ST management options.

2. RF including previous EP, previous tubal surgeries, PID, IVF, IUD, endometriosis, previous abortions are not in consideration at the time of EP management choice.

3. From our study no information about subsequent fertility was obtained because data involving future fertility was not included in patient’s history cases. According to previous fertility, no difference in choosing MTX or ST according previous IVF procedure or previous infertility diagnosed.

4. Comparing MTX and ST choice of EP treatment, a relationship was established between EP characteristics and management option. The decision to choose MTX over ST is made in cases reporting no complications, no ectopic cardiac acivity, levels of $\beta$-hCG <1000 mIU/mL, and ectopic mass size being < 4cm.
6. REFERENCES


