Ectopic Pregnancy – A Retrospective Study of Frequency, Location, Treatment Modalities and Outcomes

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SUMMARY

Ectopic pregnancy (EP) is a pregnancy complication that can be associated with high morbidity and mortality rates. Early diagnosis and right therapeutic option are crucial for good outcomes. This descriptive, retrospective single center study included 223 patients treated during the 2020-2022 period. Medical history data, ultrasound findings, β-hCG concentrations, method of treatment, response to therapy, and disease outcome were followed and statistically analyzed. Out of 223 patients, 84 EP was treated surgically, 15 expectantly, 105 with methotrexate, and 19 patients were operated on after initial attempt of treatment with methotrexate. A statistically significant difference was observed between the patients treated with methotrexate and those subsequently operated on according to the ectopic sac diameter (21.26±7.22 mm *vs*. 29.00±15.82 mm; p=0.002) and mean β-hCG level (1891.51±1451.81 *vs*. 2874.94±555.78 mIU/mL; p=0.009). EP should be considered as differential diagnosis in all women presenting with abdominal pain and vaginal bleeding after an adequate period of amenorrhea. β-hCG levels above 2000 mIU/mL and gestational sac bigger than 30 mm significantly reduce methotrexate therapy success rates.

KEYWORDS

Ectopic pregnancy; *β-hCG*; *Methotrexate*; *Laparoscopy*

Introduction

Implantation of the blastocyst outside the uterine cavity is considered an ectopic pregnancy (EP). It occurs in every 40-100 normal pregnancies. It is the leading cause of maternal mortality in the first trimester of pregnancy and contributes 6% of total maternal mortality[1,2]. The highest percentage of EP is localized in one of the fallopian tube segments (95%-97%). A smaller percentage of EP implies implantation on the cervix, uterine horns, abdominal cavity, ovaries, scar on the uterus from a previous cesarean section, and in the myometrium. A special case is heterotopic pregnancy, a combination

of intrauterine and ectopic pregnancy (extremely rare occurrence, 1:30,000 pregnancies)[1,2].

In most cases, EP results from a disturbance in fallopian tube anatomy. Previous EP carries a 10%-15% risk of recurrence. This risk is related to the underlying fallopian tube disorder that led to the first EP and to the choice of treatment method. The second most common risk factor is pelvic inflammatory disease, caused by infection with chlamydia, gonorrhea and non-specific pathogens. Other risk factors leading to EP include fallopian tube stenosis, fallopian tube reconstructive surgery, infertility, as well as assisted reproductive technology, intrauterine contraceptive devices, progesterone hormonal contraception, smoking, multiple abortions, and patients older than 35 years[1,3,4].

Clinical manifestations of EP most often occur in the period from the 6th to 8th gestational week with tubal localization. According to the course, EP can be acute and subacute. The acute course is characterized by fallopian tube rupture, resulting in profuse bleeding in the abdominal cavity, followed by sudden severe pain and cardiovascular collapse. Signs of peritoneal irritation and acute abdomen (elastic defense of the musculature, flatulence, less audible or absent peristalsis) are present in cases of profuse intra-abdominal bleeding. The subacute course is much more common, with less pronounced symptoms in the form of unilateral pain, amenorrhea, and scanty vaginal bleeding. In most cases, the classic triad of symptoms occurs, including amenorrhea (75%), abdominal pain (95%), and vaginal bleeding (60%). In addition to this classic triad of symptoms, uncertain signs of a normal pregnancy may also occur (nausea, vomiting, frequent urination, breast tenderness); however, these symptoms are rare due to lower concentrations of progesterone, estradiol, and beta human chorionic gonadotropin (β-hCG)[1,2,5].

The combination of quantitative determination of serum β-hCG and ultrasound examination of the pelvis is the most reliable diagnostic procedure for early detection of EP in hemodynamically stable patients[1,2].

Decision on the method of treatment should be based on individual factors and patient preferences, clinical findings, ultrasound findings, and β-hCG levels. If the patient is hemodynamically stable, the choice of treatment goes in the direction of conservative methods; however, if the patient shows signs and symptoms of EP rupture, then we decide on urgent surgical treatment[6]. Expectant treatment involves monitoring and controlling the patient's condition until spontaneous recovery of the tubal pregnancy occurs[3]. Medical treatment involves the use of drugs with anti-trophoblastic action. This type of therapy is indicated for healthy women in whom intrauterine pregnancy is excluded; tubal pregnancy is not greater than 40 mm; no signs of rupture and cardiac action; β-hCG is lower than 5000 mIU/mL[1,2,7]. Methotrexate is administered in a dose of 50 mg/m^2 (1 mg/kg) intramuscularly, one or two doses or according to a multi-dose protocol, with the use of Leucovorin®[1]. Certain protocols recommend two doses of methotrexate 50 mg each, 2 days apart. Such a protocol is represented at the Department of Gynecology and Obstetrics, University Clinical Center of Vojvodina (UCCV). The concentration of β-hCG should be measured before administration of the first dose of methotrexate. Its effectiveness is assessed by serial measurements on days 4 and 7, then every week until blood concentrations are undetectable. After the first dose of methotrexate, there is an initial increase in β-hCG between day 1 and day 4, and gradual decrease is noted after the first week. If there is no decrease in concentration, re-administration of methotrexate should be considered or surgical treatment should be decided[1-3,6,8]. Surgical therapy is the most common form of EP treatment[1,6]. If the pregnancy is intact and discovered while it is still in the fallopian tube, a laparoscopic approach with removal of the entire fallopian tube (salpingectomy) or only opening of the fallopian tube and removal of the conceptus (salpingotomy) is considered[1]. Classic laparotomy

or incisional approach is used in hemodynamically unstable patients with profuse bleeding, cornual or abdominal pregnancy, and unavailability of laparoscopic equipment and trained personnel[2].

Maternal death after EP is an uncommon outcome in developed countries. Maternal morbidity is associated with pain, transfusion requirements, and operative complications[5].

UCCV is a referral center for the region of Vojvodina, which counts around 2 million people. There are 6500-7000 deliveries annually in UCCV. In the absence of national guidelines for EP, variable treatment approaches are present in clinical practice.

The aim of this research was to determine the incidence of EP; which localizations of EP are most prevalent; which therapeutic methods were applied and to evaluate their success; and outcomes of EP.

Material and methods

Patients

This descriptive and retrospective study included 223 patients who were treated at the Department of Gynecology and Obstetrics, University Clinical Center of Vojvodina in the period from 2020 to 2022. The study was approved by the institutional Ethics Committee as of May 27, 2022, no. 00-120. The following data on patients with a confirmed diagnosis of EP were collected from the available medical records: history data, ultrasound findings, β-hCG concentrations, method of treatment, response to therapy, and disease outcome.

Information on how many patients had EP *per* year was obtained from medical records. History data included information on the patient's age, clinical picture, gynecologic history, previous diseases, and abdominal surgeries. Among clinical picture parameters, it was recorded whether the women had vaginal bleeding, pain in lower abdomen, nausea and vomiting when they were admitted to the department. The mean gestational age of EP at admission was calculated based on the date of the last menstrual period and date of the first examination. Data on pregnancy, parity, abortions, type of abortion, and number of previous EPs were taken from the gynecologic history.

Transvaginal ultrasonography as a diagnostic method was performed at admission. Based on this finding, we obtained information about EP localization and size of the ectopic sac. Among other things, it was noted whether fetal heart action, yolk sac and fetal echo, hematosalpinx, free fluid in Douglas pouch and pseudogestational sac were recorded. The ectopic sac size was compared with the choice of therapeutic method and treatment outcome. In patients who were treated operatively, localization of EP was confirmed from the histopathologic reports. Data on β-hCG levels at admission and follow up levels after methotrexate therapy were collected from documentation. The concentrations of β-hCG at admission were compared with the choice of therapy and outcome. Regarding therapy applied, patients were divided into four groups as follows: patients treated expectantly; patients treated with methotrexate; patients treated surgically; and patients initially treated with methotrexate but due to the lack of resolution or worsening of clinical status, treatment was eventually completed with surgical intervention. Based on the method chosen during surgical treatment, patients were divided into three groups as follows: patients who underwent laparoscopy; patients who underwent laparotomy; and patients who underwent evacuation curettage.

Based on the operative protocol and histopathologic findings, data were obtained on the outcome, fallopian tube rupture, conceptus size, bleeding in the abdominal cavity, whether the EP was intact, whether adhesions were present, and whether both fallopian tubes were removed. In the operative findings of some women, it was stated in which part of the fallopian tube the gestational sac was present.

Statistical analysis

The Microsoft Excel 2016 program was used on statistical data processing in this research. Numerical features were shown as mean values (arithmetic mean, median) and measures of variability (value range, standard deviation (SD)), and attributive features using frequencies and percentages. Comparison of numerical features between two groups was performed using Student's t-test. Testing difference in the frequencies of attributive features was performed using the χ^2-test. Values at the significance level of $p<0.05$ were considered statistically significant. Results are presented in tables and figures.

Results

This study included 223 patients diagnosed with EP who received treatment at the Department of Gynecology and Obstetrics, University Clinical Center of Vojvodina from January 2020 to June 2022. Total number of EP cases was 94 in 2020, 82 in 2021, and 47 in 2022. The mean age of patients at the time of diagnosis was 32.02±5.49 years, and mean gestational age at admission was 7.51±1.94 weeks.

Figure 1 illustrates the percentage of EP symptoms and signs observed in women upon admission. Only 1% of patients presented with all three symptoms, whereas 16% were asymptomatic.

Out of 223 patients, data on the number of previous pregnancies was available in 203 patients. The mean number of pregnancies was 2.44 (mode=1; median=2), with mean parity of 0.86 (mode=0; median=1). The rate of patients with a history of miscarriage was 28%. Table 1 shows data

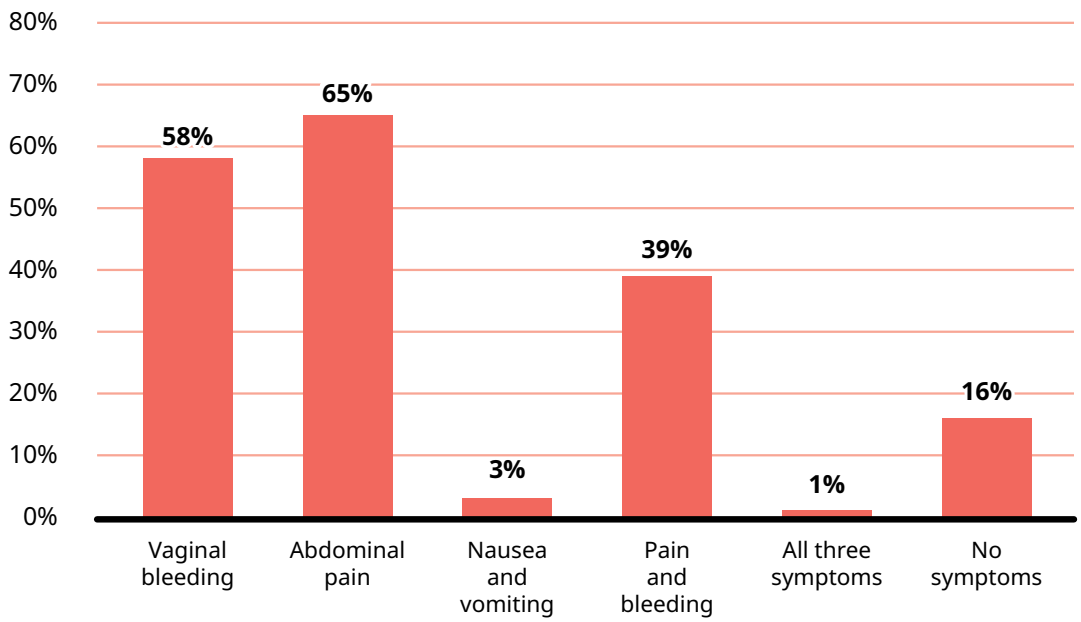


Fig. 1. Clinical signs and symptoms of ectopic pregnancy among examined patients at the time of admission.

Table 1. Number of previous pregnancies, deliveries and abortions among examined patients in absolute values and percentages

	0	1	2	3	≥4
Previous pregnancies	61 (30%)	59 (29%)	48 (24%)	21 (10%)	14 (7%)
Previous deliveries	92 (46%)	64 (32%)	36 (18%)	5 (2%)	5 (2%)
Previous abortions	141 (72%)	35 (18%)	15 (8%)	5 (2%)	

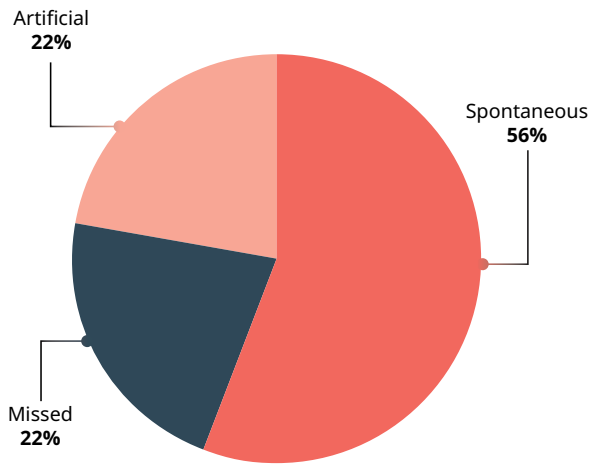


Fig. 2. Rates of different types of abortion in the group of patients who reported abortion in their history.

on previous pregnancies, deliveries and abortions. Among patients with a history of abortion, three groups were distinguished as follows: spontaneous, artificial, and missed abortion, with their percentage illustrated in Figure 2.

According to the results obtained, 20.63% of patients had one or more diseases that could be related to the occurrence of EP. The most common were the following: previous EP, hypothyroidism, insulin resistance, endometriosis, polycystic ovarian disease (PCO) and hyperprolactinemia (Fig. 3). Out of 223 patients, 28 (13.59%) had a history of previous EP. Among them, 34% were treated with methotrexate, and 66% underwent surgical treatment. Additionally, 1.45% of patients had experienced more than one previous EP.

Previous surgical interventions in the abdomen had 39.91% of patients. Table 2 shows the proportion of patients with one or more previous surgical procedures. Among patients with previous abdominal operations, the most common were cesarean

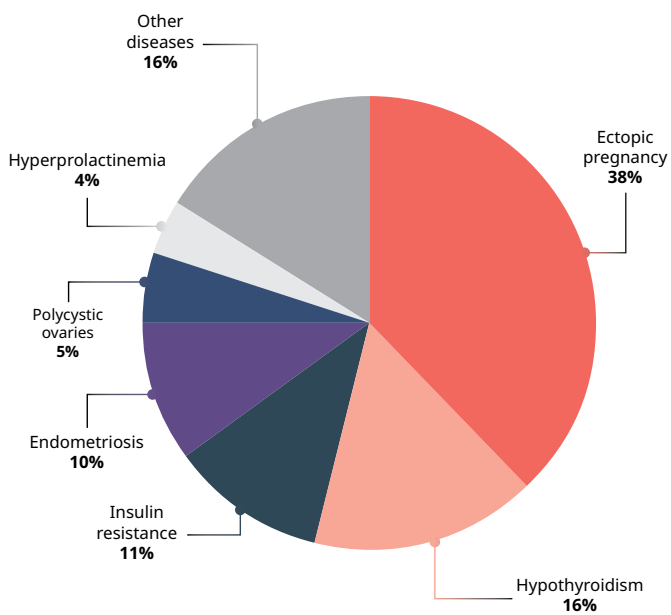


Fig. 3. Various diseases among study patients as they reported them in their history.

Table 2. Number of previous surgical procedures in the abdomen among patients who provided this history information

Number of operations	1	2	3	4
n (%)	55 (62%)	26 (29%)	5 (6%)	3 (3%)

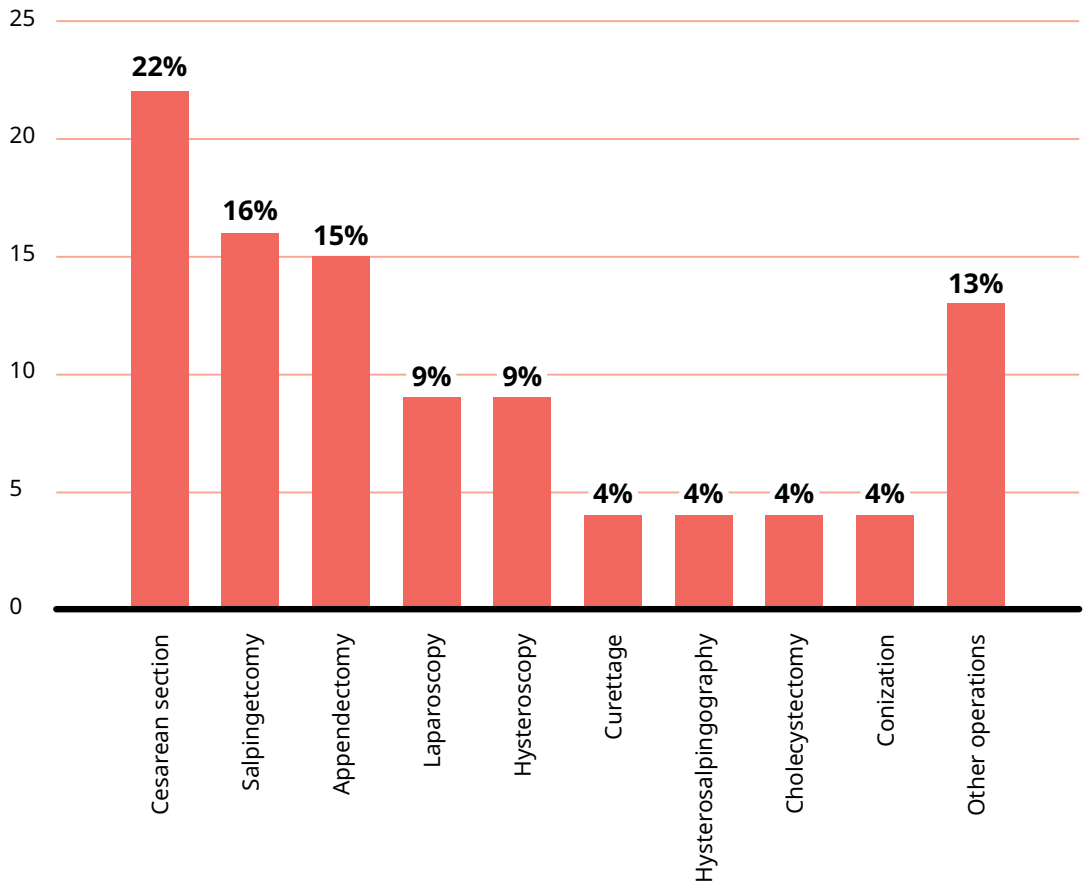


Fig. 4. Frequency of particular surgical procedures among patients who provided this history information.

section, salpingectomy, appendectomy, hysteroscopy and laparoscopic methods performed for various gynecologic conditions (Fig. 4).

Data collected from ultrasound findings are shown in Table 3. Conceptus size was recorded in 150 patients, with a mean size of 25.31±15.81 mm. Gestational sac was localized in the fallopian tube in 89.24% of cases. Other localizations were represented in a smaller percentage, as shown in Table 4. The mean β-hCG concentration measured before the applied therapy was 4067.93 mIU/mL (median=1993; SD=6688.95).

Figure 5 shows representation of patients by group based on the choice of therapy. Out of 124

Table 3. Different ultrasound findings in patients with ectopic pregnancy

	n (%)
Free pelvic fluid	94 (42.34)
Pseudogestational sac	16 (7.20)
Cardiac activity of the fetus	28 (12.60)
Yolk sac	45 (20.27)
Hematosalpinx	31 (13.96)

Table 4. Localizations of ectopic pregnancy

	%
Right fallopian tube	54.71
Left fallopian tube	34.53
Horn of the uterus	4.48
Ovary	0.89
CSP	0.44
Cervix	0.44
Abdomen	0.44
Unknown localization	4.03

CSP = cesarean scar pregnancy

(55.6%) patients who received methotrexate, only 2 patients received one dose, whereas other patients received two doses of 50 mg each, two days apart. Patients who received a single dose of methotrexate had β-hCG levels lower than 300 mIU/mL. A total of 103 (46.18%) patients had operative treatment, of which 99 had laparoscopy. In 3 patients, it was decided to convert to laparotomy, so a total of 6 patients underwent laparotomy, and one patient underwent evacuation curettage. Evacuation curettage alone was performed in a patient with cervical pregnancy. Abdominal pregnancy was treated laparoscopically, whereas cesarean scar pregnancy was treated with methotrexate. Ovarian EPs were treated expectantly and with methotrexate.

The mean age of patients treated with methotrexate was not statistically significantly different compared to patients who were subsequently treated surgically (32.41±5.30 *vs.* 32.36±4.64; p=0.48). The youngest patient who received methotrexate was 20 years old, and the oldest was 45 years old. Among patients who were subsequently operated on, the youngest was 24 years old, and the oldest was 39 years old. These two groups of patients were also compared according to gestational age, but without a statistically significant difference (7.36±1.01 *vs.* 7.55±1.46; p=0.29). Using the χ^2-test, we compared EP localization in patients who underwent surgery compared to patients who were treated surgically after methotrexate therapy and found that there was no statistically significant difference between these two groups according to localization (right fallopian tube *vs.* left fallopian tube; 59.7% *vs.* 63.1%; p=0.78). Patients were compared based on the choice of therapeutic method and information on whether abdominal pain

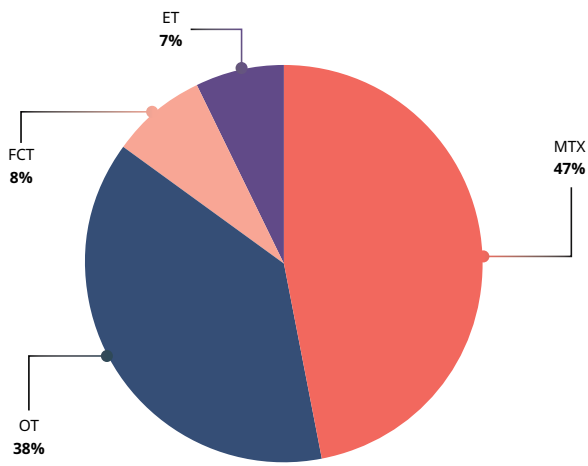


Fig. 5. Rates of different treatment options.

MTX = methotrexate; OT = operative treatment; FCT = failed conservative treatment; ET = expectant treatment

and vaginal bleeding were present at admission. A statistically significant difference was observed in patients who had abdominal pain according to the choice of therapy (p=0.0062). However, there was no significant difference in vaginal bleeding (methotrexate 59% *vs*. operative 53.6% *vs*. both methods 68.4% *vs*. expectant 66.7%; p=0.56). According to the presence of abdominal pain, the following groups of patients were compared: pain was less prevalent in patients who were treated with methotrexate compared to patients who were treated surgically (54.3% *vs*. 78.6%; p=0.0005); patients who were treated with methotrexate with patients who subsequently underwent surgery (54.3% *vs*. 68.4%; p=0.25); and patients who were immediately operated on with patients who were subsequently treated operatively (78.6% *vs*. 68.4%; p=0.34). Comparison was made based on the presence of hematosalpinx on ultrasound findings with the treatment method. We found that patients who were treated operatively had more hematosalpinx compared to patients who were treated with methotrexate, operatively after methotrexate administration, and expectantly (24.1% *vs*. 5.7% *vs*. 10.5% *vs*. 13.3%; p=0.003). Using the χ^2-test, we compared patients who had previous abdominal surgeries in relation to whether they were treated with medication, surgery, or both methods (Table 5).

Table 5. Differences among patient groups treated with methotrexate, surgically, and both methods in relation to previous abdominal surgery (χ2-test)

Operation	Treatment	Yes	No	p
Cesarean section	Methotrexate	13	92	0.27
	Operation	7	77	
	FCT	4	15	
Appendectomy	Methotrexate	8	97	0.91
	Operation	7	77	
	FCT	2	17	
Salpingetcomy	Methotrexate	10	95	0.82
	Operation	7	77	
	FCT	1	18	
Laparoscopy	Methotrexate	1	104	**0.0006***
	Operation	5	79	
	FCT	4	15	
Cholecystectomy	Methotrexate	2	103	0.79
	Operation	2	82	
	FCT	0	19	

p = level of statistical significance;*parameter is statistically significant; FCT = failed conservative treatment

Table 6. Mean, minimum and maximum β-hCG levels and standard deviation according to therapy

Treatment	Mean (mIU/mL)	SD (mIU/mL)	Min (mIU/mL)	Max (mIU/mL)
Methotrexate	1891.51	1451.81	205	5599
Operation	7866.41	9823.83	2	45371
Failed conservative treatment	2847.94	555.78	501	6502
Expectant management	618.68	591.26	76	2304

SD = standard deviation; Min = minimum; Max = maximum

Table 7. Mean, minimum and maximum values of ectopic sac diameter and standard deviation according to therapy

Treatment	Mean (mm)	SD (mm)	Min (mm)	Max (mm)
Methotrexate	21.26	7.22	11	48
Operation	31.19	12.58	10	60
Failed conservative treatment	29	15.82	12	70
Expectant management	25.25	6.69	20	37

SD = standard deviation; Min = minimum; Max = maximum

According to the outcome of surgical treatment on the fallopian tubes, salpingectomy was performed in 99 patients, salpingotomy in one patient, and adnexectomy in one patient. Table 6 presents the mean, minimum, and maximum β-hCG levels with SD in relation to the applied therapy. In patients treated with methotrexate, the mean β-hCG levels were statistically significantly lower compared to those measured in patients who underwent subsequent surgical treatment (1891.51±1451.81 *vs*. 2874.94±555.78 mIU/mL; p=0.009). A statistically significant difference was also observed between patients who were immediately treated operatively and those who were subsequently treated surgically (7866.41±9823.83 *vs*. 2874.94±555.78 mIU/mL; p=0.02). During monitoring of β-hCG follow up levels after methotrexate administration, an increase in this hormone was observed in 33.33% of patients in whom this therapy was successful, with a mean increase by 34.44%. In 53.33% of patients who underwent subsequent surgery, a 55.55% β-hCG rise was recorded.

The mean, minimum, and maximum values of ectopic sac diameter with SD according to therapy applied are presented in Table 7. Using Student's t-test, it was determined that the mean diameter of the ectopic sac was statistically significantly smaller in patients who received methotrexate compared to patients who underwent subsequent surgical treatment (21.26±7.22 mm *vs*. 29.00±15.82 mm; p=0.002). However, there was no statistically significant difference in the mean diameter between the group of patients who underwent immediate surgery and those who underwent surgery later (31.19±12.58 mm *vs*. 29.00±15.82 mm; p=0.30).

Table 8 displays data collected from the operative protocol. Additionally, information regarding the gestational sac location within the fallopian

Table 8. Intraoperative finding

	Intact	Rupture	Adhesions	Hemorrhage	Both fallopian tubes damaged
%	53.39	14.56	39.80	62.13	7.76

tube was extracted from the operative protocol, and these data were available on 53 patients. The findings revealed that in 11 patients, the sac was situated in the distal part, in 15 patients in the central part, and in 27 patients in the proximal part of the fallopian tube.

The χ^2-test was utilized to compare patients who experienced rupture, bleeding, and adhesions during operative treatment based on whether they were treated immediately or subsequently. However, no statistically significant difference was found between these groups. The p-values on patients who experienced rupture, bleeding, and adhesions were 0.58 (15.5% *vs*. 10.5%), 0.91 (61.9% *vs*. 63.1%), and 0.2 (36.9% *vs*. 52.6%), respectively.

It is noteworthy that no maternal deaths were recorded in this study.

Discussion

The study revealed a mean of annual EP diagnosis in 89.2 patients, with a mean age of 32.02 years. The mean gestational age of EP at the time of presentation to the Deparment was 7.51 weeks. No significant age or gestational age differences were observed between patients treated with methotrexate and those who underwent surgery (p=0.48 and p=0.29, respectively), which is consistent with previous research[8-11].

Abdominal pain was the most prevalent symptom, occurring in 65% of cases, followed by vaginal bleeding in 58% of patients. Both symptoms were reported by 39% of patients. Patients presenting with abdominal pain exhibited significant differences in treatment choices (p=0.0062), particularly between methotrexate and operative treatments (p=0.0005), suggesting a preference for surgery in such cases. However, no significant differences were noted regarding other treatment modalities. The presence of vaginal bleeding did not significantly influence treatment decisions (p=0.56). Nausea and vomiting were reported in 3% of cases. All studies consistently report a significant association between vaginal bleeding and abdominal pain with the presence of EP. Therefore, suspicion of EP is warranted in all women presenting with pain and bleeding following a period of amenorrhea[8,9,11-13].

Two-thirds of EP cases occur in multigravid women, making multipregnancy a recognized risk factor for EP development. Our study revealed a mean of 2.44 pregnancies and parity of 0.86. Notably, 30% of women experienced their first pregnancy, while 70% had one or more pregnancies, and 46% were nulliparous. These findings suggest that a significant number of pregnancies did not result in childbirth, supported by the fact that 28% of patients had one or more abortions in their history and this can be related to the subsequent occurrence of postoperative complications, such as infections and adhesions. Spontaneous abortion was most common and may have a causal effect on the occurrence of EP due to chromosomal abnormalities or hormonal imbalance, which also are risk factors for EP. However, further research is needed to explore this relationship[8,9,11,12].

Analysis of the results revealed that several diseases were prevalent in patient history, including

previous EP (38%), hypothyroidism (16%), insulin resistance (11%), endometriosis (10%), PCO (5%), and hyperprolactinemia (4%). In total patient population, 13.59% had a history of previous EP, aligning with existing studies suggesting a correlation between underlying conditions leading to the initial EP and the choice of treatment method. Notably, 34% of patients with a history of EP were treated with methotrexate, while 66% underwent surgery, with no instances of expectant treatment observed. The high rate of EP after salpingectomy due to previous EP can be interpreted in two ways. Firstly, the macroscopically normal appearance of the contralateral fallopian tube does not exclude underlying pathology that may have precipitated the initial EP. Additionally, the availability of *in vitro* fertilization services in Serbia (fully covered unlimited number of attempts for the first common child) may influence patients and physicians to opt for more radical surgical approaches in treating EP. Studies have yielded divergent results regarding the treatment associated with the highest risk. Factors potentially linking increased endometriosis incidence with EP include the development of tubo-ovarian adhesions, fallopian tube lesions, and alterations in the ovarian-fallopian tube relationship. Future investigations should consider the localization of endometriosis to validate these assertions. Limited literature exists on the association of other diseases with EP, warranting further research in this area[10,14-17].

A significant portion (39.91%) of patients had undergone one or more previous abdominal surgeries. The high prevalence of previous operations can largely be attributed to cesarean sections (22%), which have been increasing in incidence annually. Among other operations, salpingectomy and appendectomy were most common. Statistical significance was observed in patients with a history of laparoscopic intervention regarding therapy applied, suggesting a higher tendency of surgical treatment in such cases (p=0.0006). This finding is consistent with previous studies indicating that prior surgical procedures represent a significant risk factor[10,11].

The presence of an intact gestational sac significantly aids in the early diagnosis of EP. In its absence, an adnexal mass may be mistaken for a corpus luteum cyst. Visualization of the yolk sac and embryo echo outside the physiological site of implantation, particularly with fetal heart activity, serves as a reliable indicator of EP. Yolk sac and embryo echo were visible in 20.27% of patients, consistent with other studies. Fetal heart activity was recorded in 28 women, with only one treated with methotrexate, indicating its importance in treatment choice. Ultrasound findings revealed a pseudogestational sac in 7.2% of cases, underscoring that its absence does not exclude the diagnosis of EP. It was concluded that the presence of hematosalpinx is an indication for operative treatment, as indicated by the statistically significant difference between the presence of hematosalpinx and choice of therapy (p=0.003). Free fluid in the Douglas pouch, potentially indicating the presence of blood, was noted in 42.34% of cases in this study. In comparison to other studies, this percentage was lower, suggesting that patients in this study may have had milder forms of EP or were diagnosed earlier[12,17,18].

Fallopian tubes were the most common localization of EP, present in 89.24% of cases. Most studies have concluded that the right fallopian tube has a higher incidence than the left one, which was confirmed by our research. No difference was found between patients who underwent immediate surgical treatment and those who underwent surgery after methotrexate therapy according to localization of the ectopic sac in the left or right fallopian tube (p=0.78). This study observed a slightly lower percentage of tubal pregnancies compared to other researches, with a higher representation of cornual pregnancies (4.48%). One possible explanation is that pregnancies in the isthmic or interstitial segment of the fallopian tube were classified as cornual. Other less common localizations

included the ovaries, cervix, cesarean section scar, and abdomen. Cases where pregnancy localization could not be determined by ultrasound, despite elevated β-hCG levels, were diagnosed as pregnancies of unknown localization, accounting for 4.03% of cases in this study. There is a possibility that abnormal intrauterine pregnancies were not visible on ultrasound[11,12,19-22].

Based on the operative protocol, it was found that the gestational sac during tubal pregnancy was most commonly located in the distal part, corresponding anatomically to the ampullar part of the fallopian tube, which aligns with the most common location of EP according to the literature[1,2,12].

The mean size of the gestational sac measured by ultrasound was 25.31 mm. Comparing the size of the gestational sac in relation to the applied therapy revealed that the largest mean diameter was observed in women who underwent surgical treatment (31.19 mm), while the smallest was found in women treated with methotrexate (21.26 mm). Patients initially treated with methotrexate but later undergoing surgery had an average diameter of 29 mm, which is approximately equivalent to those who underwent immediate surgical intervention. A statistically significant difference in diameter was observed between patients treated with methotrexate and those subsequently operated on (p=0.002). This suggests that the size of the gestational sac can be an important factor in determining appropriate therapy. Helmi *et al.* reached similar conclusions, although they did not observe statistical significance[3,9,23-25,27].

The mean measured concentration of β-hCG in all patients before therapy was 4067.93 mIU/mL. However, when comparing β-hCG levels with the therapy received, it was found that patients who underwent surgery had the highest β-hCG levels (7866.41 mIU/mL), while those treated expectantly had lowest β-hCG levels (618.68 mIU/mL), as expected given the significance of this hormone in therapy choice. Patients treated with methotrexate (1891.51 mIU/mL) had levels within the treatment guidelines recommended by the literature. In patients treated with both medical and surgical approaches, the mean β-hCG level was 2847.94 mIU/mL, suggesting that levels above 2000 mIU/mL decrease the probability of medical therapy success. A statistically significant difference was observed between patients treated with medication and those subsequently treated surgically according to the mean β-hCG levels (p=0.009). Similarly, patients who underwent immediate surgery and those who underwent surgery after methotrexate therapy showed differences (p=0.02). In one-third of the women treated with methotrexate, an increase in β-hCG was observed after therapy, averaging 34.44%, with positive outcomes observed in all patients. Other researchers suggest that if β-hCG levels increase by more than 50%, it may indicate failed drug therapy, prompting consideration of surgical intervention, a finding corroborated by our research, where 53.33% of subsequently operated patients experienced a β-hCG increase by 55.55%[1,3,6,24,26].

Methotrexate emerged as the therapy of choice for many patients, contrasting with other studies where surgical treatment prevailed. This outcome aligns with earlier diagnoses and milder clinical presentations in patients. Expectant treatment was the least common, consistent with existing research. However, methotrexate treatment was unsuccessful in 15% of women. Current literature suggests a seven-day administration of gefitinib alongside a single methotrexate dose, potentially avoiding surgical intervention in stable patients. Only two patients received a single methotrexate dose due to β-hCG levels below 300 mIU/mL, while the remaining followed a two-dose protocol administered two days apart. Some researchers suggest the single-dose protocol has a slightly lower success rate, albeit with fewer side effects and lower costs compared to the multi-dose regimen, which requires more intensive monitoring[9,12,21,26,27].

Among the patients treated operatively, laparoscopy was performed in 96 cases, reflecting a growing preference for laparoscopic methods with

increasingly favorable outcomes, as suggested by recent studies. Laparotomy was conducted in six patients, while one patient underwent evacuation curettage. Conversion from laparoscopy to laparotomy occurred in three cases, indicating a high laparoscopic success rate. Salpingectomy was the most common procedure, with both fallopian tubes removed in 7.76% of cases, reflecting divergent opinions observed in other studies. Adnexectomy and salpingotomy were performed in one patient each. Most studies suggest that their results indicate salpingectomy, when performed, does not significantly impact future fertility of the mother compared to salpingostomy[12,21,26,27,29].

During surgery, it was noted that the pregnancy remained intact in 53.39% of women, with 14.56% experiencing ruptured fallopian tubes. Our rate of tubal rupture was lower than in other recent studies, suggesting that routine transvaginal sonography aids in early diagnosis, allowing for treatment before tubal rupture occurs. Additionally, no difference was observed between patients immediately treated surgically and those operated on after methotrexate administration regarding the presence of rupture during surgery (p=0.58). Bleeding in the Douglas pouch was reported by 62.13% of women. Peritubal adhesions were found in 39.8% of patients undergoing surgery, a rate lower than in other studies, potentially related to prior pelvic inflammatory diseases and abdominal surgeries. The literature suggests that maternal mortality due to EP ranges from 0 to 1.3%; however, in our research, no fatal outcomes were recorded[9,11,29,30].

In Serbia, there is no national guideline published for ectopic pregnancy. Instead, clinicians are guided by the recommendations of international associations. At UCCV, decision on the best treatment option for the patient with EP is made individually according to the symptoms, β-hCG levels, and ultrasound findings. In Vojvodina region, surgical treatment was dominant treatment option for EP. However, in recent years much effort has been made to expand early EP diagnosing and application of conservative treatment. ACOG and FIGO recommendations are followed for methotrexate use: β-hCG <5000 mIU/mL, gestational sac <30 mm, and no signs of intra-abdominal bleeding. Failure rate of methotrexate was reported as 14.3% when β-hCG >5000 mIU/mL, but less than 3.7% for β-hCG <5000 mIU/mL in a systematic review[7]. Smaller studies recommended cut-off level of β-hCG <3000 mIU/mL for better success of conservative treatment[3]. In our research, failure rate of methotrexate treatment was 8%. This higher failure rate for smaller β-hCG levels could be explained by different interpretation of the symptoms during follow up. Namely, it is known that several days after application of methotrexate, moderate pelvic pain and small amount of free fluid can be seen. In some cases, this could be misinterpreted as worsening of clinical status and lead to the indication for surgery. All of this indicates that a more advanced system for decision-making is needed, which could be provided by new technologies such as machine learning[31].

This research, conducted retrospectively, had inherent limitations, including the inability to collect comprehensive data for all EP cases during the study period. Additionally, the study was limited to the UCCV and did not encompass data from the entire country.

Conclusion

In conclusion, it is an imperative for clinicians to maintain a high index of suspicion of EP in all women of childbearing age, as early detection is paramount for reducing female morbidity and enhancing treatment efficacy.

The study results underscored several well-established risk factors for EP, including a history of abortions, prior EP, abdominal surgeries, and maternal age over 30 years. Therefore, clinicians

should include EP in the list of differential diagnoses for any woman presenting with abdominal pain and vaginal bleeding after an appropriate period of amenorrhea.

Serial monitoring of β-hCG levels and transvaginal ultrasonography remain the cornerstone for diagnosing EP. While tubal pregnancies were most prevalent, other ectopic sites were slightly more prevalent than reported in previous studies.

Expectant and medical management represent safe and effective options for clinically stable and asymptomatic women, particularly when carefully selected. Laparoscopy emerges as the preferred surgical approach, with salpingectomy demonstrating superior outcomes over salpingotomy. This study reflects a growing trend among clinicians to favor more conservative treatment modalities, with methotrexate showing promising success rates. However, β-hCG levels exceeding 2000 mIU/mL and ectopic sac bigger than 30mm significantly diminish the efficacy of methotrexate therapy. Ultimately, clinical presentation, ectopic sac size, β-hCG concentration, fetal cardiac activity, and patient preferences should all be considered when determining the appropriate therapeutic approach. These factors play a pivotal role in treatment success, future fertility prospects, and the risk of EP recurrence. ■

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SAŽETAK

Ektopična trudnoća – retrospektivno istraživanje učestalosti, lokacije, načina liječenja i ishoda

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Ektopična trudnoća (ET) je komplikacija u trudnoći povezana s visokim stopama majčinskog pobola i smrtnosti. Rana dijagnoza i pravi terapijski izbor ključni su za povoljan ishod. Ova deskriptivna, retrospektivna studija provedena u jednom centru obuhvatila je 223 bolesnice liječene u razdoblju od 2020. do 2022. godine. Praćeni su i statistički obrađeni anamnestički podaci, ultrazvučni nalazi, koncentracije β-hCG, način liječenja, odgovor na terapiju i ishod bolesti. Ukupno je bilo 223 slučaja ET, od kojih je 84 liječeno kirurški, 15 ekspektativno, 105 metotreksatom, dok je 19 žena operirano nakon početnog pokušaja liječenja metotreksatom. Uočena je statistički značajna razlika između bolesnica liječenih metotreksatom i naknadno operiranih u odnosu na promjer ektopične vrećice (21,26±7,22 mm prema 29,00±15,82 mm; p=0,002) i prosječne vrijednosti β-hCG (1891,51±1451,81 prema 2874,94±555,78 mIU/mL; p=0,009). ET treba razmotriti kao diferencijalnu dijagnozu u svih žena koje imaju bolove u trbuhu i vaginalno krvarenje nakon odgovarajućeg razdoblja amenoreje. Vrijednosti β-hCG iznad 2000 mIU/mL i gestacijska vrećica veća od 30 mm značajno smanjuju uspješnost terapije metotreksatom.

KLJUČNE RIJEČI

Ektopična trudnoća; *β-hCG*; *Metotreksat*; *Laparoskopija*