

## Factors Affecting the Management, Clinical Course and Treatment Outcome of Ectopic Pregnancy



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### ABSTRACT

**Background:** The aim of this study is to determine the incidence, clinical characteristics, treatment options and outcomes of ectopic pregnancy.

**Methods:** In this study, a total of 474 ectopic pregnancy cases that was diagnosed and treated between 2011 and 2017 were retrospectively evaluated. All the related information including the details of demographic characteristics, clinical symptoms and findings, diagnostic tools used, treatment options, risk factors for ectopic pregnancy, outcome of treatment as well as associated morbidity and mortality were obtained from hospital patient database and saved in structured data entry forms designed for this purpose. Ectopic pregnancy was diagnosed on direct ultrasound signs associated with an empty uterus and positive  $\beta$ -Hcg or on clinical signs associated with an empty uterus and suggestive  $\beta$ -hCG kinetics over several days.

**Results:** A total of 6462 deliveries with 492 ectopic pregnancy diagnoses recorded and 474 of them were eligible for study and the incidence of ectopic pregnancy was found 7.6%. A great majority of the patients who constituted the study group was between 25-34 years 62.4% (296/474) and 31.6% (150/474) was primigravida. Abdominal and/or pelvic pain and amenorrhea were most consistent symptoms in 54 % and 24% of women respectively. Medical treatment with single dose methotrexate was applied to 342 (%72.2) patients and surgery was performed to 116 (24.5%) patients at first. Among the EP patients a death was observed.

**Conclusion:** Ectopic pregnancy still considered being a major health problem so greater emphasis should be laid on prevention and early detection as to give patients opportunities for tubal conservation and decreasing surgical requirement.

### KEYWORDS:

Ectopic pregnancy,  
Methotrexate,  
Surgical management,  
Salpingectomy,  
Salpingostomy

**I. INTRODUCTION**

Ectopic pregnancy (EP) is a life-threatening pregnancy complication occurring in approximately 2% of all pregnancies [1]. The incidence of ectopic pregnancy is increasing in developed countries [2]. However, early diagnosis has seriously reduced mortality and morbidity due to illness. In addition to acute morbidity, ectopic pregnancy may decrease future fertility. The risk of ectopic pregnancy in women who have abnormal fallopian tubes is increased [3]. Other risk factors, such as sexually transmitted diseases, pelvic inflammatory disease, history of ectopic pregnancy, infertility, abdominal cavity or pelvic surgery, endometriosis, previous surgery on fallopian tubes, smoking and maternal age, increase the risk of ectopic pregnancy. Many non-surgical treatments have been used; however, in recent years, intramuscular methotrexate has been considered due to easy administration, its less invasive nature, low complications and low cost [4].

There is considerable regional variation in EP incidence and there is a significant rising global trend over the past decades. But despite its increasing incidence, the chances of early diagnosis have increased and mortality associated with ectopic pregnancy have decreased from 19.6/10.000 to 3.4/10.000 due to common applications of transvaginal ultrasound (USG), minimally invasive surgeries and sensitive laboratory quantitative human chorionic gonadotropin measurements [5]. Unfortunately this decline is apparent especially in developed countries. In developing countries; a majority of hospital-based studies have reported EP case-fatality rates of around 1%–3%, 10 times higher than those reported in countries with developed economies and health systems [6]. The management options depend on the symptoms, the  $\beta$ -hCG level, the ultrasound findings, the patient's general health and preferences, and the facilities for follow-up. Surgical treatment most commonly consists of either salpingectomy or salpingostomy with tubal preservation. With conservative management via methotrexate or salpingostomy, close follow up with serial measurements of quantitative  $\beta$ -hCG is imperative to ensure resolution [7]. Although the rate of medical management with methotrexate is increasing, among women who undergo surgery, tubal-conserving salpingostomy is being used less frequently [8].

The aim of this retrospective study is to determine the incidence, clinical characteristics, prognostic factors affecting treatment outcomes and different management options in patients with a diagnosis of ectopic pregnancy. For this reason, patients who were diagnosed as EP at our institution were retrospectively evaluated.

**II. METHODS**

This retrospective study was conducted on 474 women with ectopic pregnancy who were admitted to Department of Obstetrics and Gynecology at Kafkas University in Kars, Turkey and who had treatment for ectopic pregnancy with one or more doses of methotrexate 50 mg/m<sup>2</sup> or surgical procedure between 2011 and 2017.

The medical data of each patient was obtained from the hospital records, discharge summaries and operation notes. The initial  $\beta$ -hCG levels and size of ectopic pregnancy mass in vaginal sonography, treatment options, risk factors for EP, the details of demographic characteristics, clinical symptoms and findings, outcome of treatment as well as associated morbidity and mortality were recorded in the questionnaire. All patients had a series of pretherapeutic laboratory tests including  $\beta$ -hCG, complete blood count, coagulation, liver function, serum creatinine, blood group and irregular antibody screening.

Endometrial sampling was performed from all the patients who were taken into the study except seven heterotopic and one who was died and patients who could not be diagnosed as ectopic pregnancies histopathologically were not included in the study. Eighteen patients were excluded from the study: twelve who had incomplete medical files as concerns the data necessary for the study or who were rapidly lost to follow-up, four patients without endometrial sampling and two patients with renal insufficiency. We contacted the 473 patients by phone and asked them about their fertility. The study was approved by the local research ethics committee(80576354-050-99/49, 01/03/2017) and informed consent was obtained from all patients except one.

**III. STATISTICAL ANALYSIS**

The process involved descriptive statistics and data were presented as mean  $\pm$  standard deviation, median and ratio. Non-parametric Mann-Whitney U test was used to compare the mean of the data among the groups. P <0.05 was considered significant. Statistical Package for Social Sciences (SPSS) for Windows 20 (SPSS for Windows, SPSS, Chicago) was used for statistical analysis.

**IV. RESULTS**

During the six-year-period, a total of 6462 deliveries were occurred in our university hospital and 474 cases of EP which were eligible for study diagnosed and treated. The incidence of EP was found 7.6 % (492/6462 deliveries). The proportion of pregnant women in the adolescent age group was 3.8% while the rate of pregnant women over 35 years was 8.9%. 62.4% of ectopic pregnancies were in the 25 -34 age group. The mean age of pregnancies is 28.95  $\pm$  4.82 (Table-1).

**Table-1: Demographic characteristics of ectopic pregnancy patients**

Age group (years)	Number (n=474)	(%)
19 age and below	18	3.8
20–24	118	24.9
25–29	148	31.2
30–34	148	31.2
35 age and above	42	8.9
<b>Gravida</b>		
1	150	31.6
2	162	34.2
3	86	18.1
4 and over	76	16.1
<b>Parity</b>		
0	180	38.0
1	184	38.8
2	84	17.7
3 and over	26	5.4
<b>Abortus</b>		
0	376	79.3
1	70	14.8
2 and over	28	5.9
<b>Total</b>	<b>474</b>	<b>100.0</b>

Although previous abdominal /pelvic surgery and dilation and curettage history was found to be a significant factor contributing to EP development, it was not at all unimportant that we could not identify any risk factors (16%) (Table 2). A history of ectopic pregnancy was noted for 38 (8%) of the women. The ectopic pregnancies occurred in the setting of assisted reproduction for 18 (3.8%) cases, 13 of which were in vitro fertilizations. Abdominal and/or pelvic pain and amenorrhea was most consistent symptoms in 54% and 24% of women respectively. Vaginal bleeding was seen in 12% of EP patients (Table 3).

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**Table-2: Relation between histories of risk factors of ectopic pregnancy**

Risk Factors	Number (n=474)	(%)
Previous pelvic surgery	126	26,6
Dilation and curettage history	86	18,1
Pelvic inflammatory disease	52	11
Previous ectopic pregnancy	38	8
History of infertility	18	3,8
Endometriosis	14	3
Presence of a coil	64	13,5
No known risk factors	76	16
<b>Total</b>	<b>474</b>	<b>100.0</b>

**Table -3: Clinical presentation of Ectopic Pregnancy patients at diagnosis**

Clinical presentation	Number (n=474)	%
Pelvic/abdominal pain	254	54
Amenorrhoea	114	24
Vaginal bleeding	56	12
Breast tenderness, nausea	10	2
Diarrhoea and vomiting	8	1,6
Pain on defecation or rectal pressure	8	1,6
Shoulder tip pain shortness of breath, lower chest pain	7	1,4
Dizziness, fainting or syncope	8	1,6
Dysuria, urinary frequency	9	1,8

The most common contraception method among EP patients was found to be coitus interruptus (56.5%) followed by condom (20.2%) and intrauterine device (13.5%). Ectopic pregnancies occurred in a setting of apparent modern contraception failure for 206 (43%) women (Table 4).

**Table 4: Contraception methods among Ectopic Pregnancy patients**

Contraception method	Number (n=474)	%
Oral contraceptive pills	7	1,5
Intrauterine device	64	13,5
Condom	96	20,2
Tubal ligation	18	3,8
Emergency contraception	21	4,5
No contraception +/- Coitus interruptus	268	56,5

According to treatment modalities, expectation was applied in only 16 (3.3%) patient. Medical treatment with methotrexate was applied to 342 (72.2%) and surgery was performed to 116(24.5%) patients. Thirty patients received both medical and surgical treatments (Table 5). When we looked at ectopic pregnancies according to residential areas, followed by tubal localization, cesarean section scar ectopic pregnancy rate was second with 3.8%. Nine women were diagnosed with heterotopic pregnancy (1.9%). We had a positive result in 4 cases of spontaneous follow-up and 6 of them started methotrexate and we got 2 remission and 4 of them went to surgery. A total of 10 patients were treated surgically, 6 primarily and 4 after the methotrexate failure.

Treatment options	Number (n=474)	%	Number (n=474)	%	Pregnancy	EP	Successful Pregnancy		
Medical treatment (Methotrexate)	342	72.2	Single dose	342	72.2	96	18	78	
			Multiple dose	18	3.8	0			
Surgery	Laparoscopy	87	24.5	Salpingectomy	72	15.2	22	1	21
				Salpingostomy	14	3	6	2	4
				Oophorectomy	1	0.2	0		
	Laparotomy	29		Salpingectomy	18	3.8	4	0	4
				Salpingostomy	9	1.9	3	2	1
				Oophorectomy	2	0.4	0		
Medical+surgery	30	6.3	30	6.3	3	0	3		
Expectation	16	3.4	16	3.4	1	0	1		
<b>Place</b>	<b>Number (n=474)</b>		<b>Number (n=474)</b>	<b>%</b>	<b>Table-5:</b> Treatment options and place of ectopic pregnancy patients in cases of surgical procedure and pregnancy rate after EP.				
Tubal	420	88.6	ampulla	378				79.7	
			isthmic	20				4.3	
			fimbria	22				4.6	
Cervical	14	3	14	3					
Ovarian	3	0.6	3	0.6					
Cesarean scar	18	3.8	18	3.8					
Interstitial	10	2.1	10	2.1					
Heterotopic	9	1.9	9	1.9					

When we examined pregnancy rates after ectopic pregnancies; we did not consider 84 patients because they were in the last year. Given that a total of 150 patients (42 in the surgical group, 94 in the methotrexate group, 12 in the methotrexate and surgery group, 1 in the expectan group and 1 was died) were not desire for future pregnancy so they were excluded from analysis and 56.2% (135/240) of the patients who had ectopic pregnancy were conceived. In a single dose methotrexate given group, 18 recurrent ectopic pregnancy and 78 normal pregnancies were achieved. Of patients with EPs, the likelihood of future intrauterine pregnancy was high; although not statistically significant, especially in the surgical group 83 % (112/135). A total of 39 pregnancies were observed in the surgical group, 5 of which were ectopic pregnancies and 30 of which were normal pregnancies.

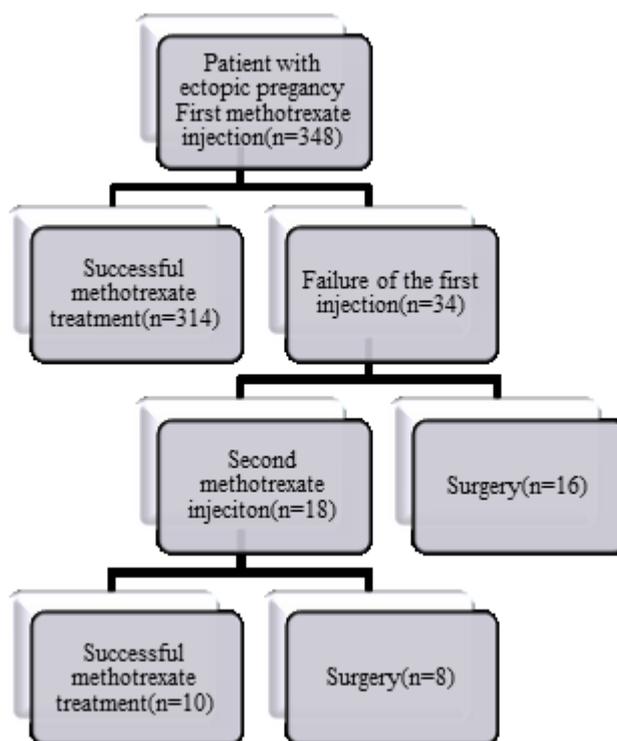
The recurrence rate of EP was 8 % following either medical or surgical management in the present study. 56.4% of our cases have one or more cesarean section (258/474).

**Table-6: β-hCG values, the Focus Size and fetal heartbeat of EP patients**

β-hCG values (IU/ml)	Number (n=474)	%	Focus size (cm)	Number (n=474)	%	β-hCG values (IU/ml)	Fetal heartbeat	Number (n=474)	%
5-1500	148	31.2	<3.5	146	30.8	4094±864	positive	116	24.4
1501-3000	156	33							
3001-4500	72	15	≥3.5	198	41.7	9118±2412	negative	358	75.6
4501-6000	34	7							
6001-7500	22	5	No Visible focus	130	27.5	760±480			
7501-10000	30	6.3							
≥10000	12	2.5							

The majority of patients had β-hCG values between 1501-3000 (33%). There were 344 cases of echographically visible tubal pregnancies and 130 cases for which the tubal location could not be affirmed by echography. In 30.8% cases focus size were 3.5 cm or more (n=146) and focus size were less than 3.5 cm in 41.7% (n=198) of cases. 16% (n=32) of patients whose focus size were less than 3.5 cm, rupture was found at the time of the diagnosis this rate was 37.3% (n=74) of patients whose focus size was 3.5 cm or more. In patients with less than 3.5 cm focus, the most common form of treatment was MTX 86% (222/258). The success of a single dose MTX treatment was 96.4% (214/222). In 474 cases positive fetal heartbeat ratio was 24.4% (n=116). The surgical procedure was applied to 92 patients (%79.3). Single dose MTX failure was seen 66.6% of cases which fetal heartbeat was positive and no surgical procedure done initially (16 of 24 cases).

**Figure-1:Flow chart for the methotrexate treatment**



A single methotrexate dose was sufficient for 90.2% of the women and a second dose was successful for 55.5% of the remaining women. Overall, the success rate of methotrexate treatment in ectopic pregnancies was 93.2%. Methotrexate therapy was failed in nine (23.6%) of 38 of previous ectopic patients and 15(4.8%) of 308 first-time ectopic patients. All the failed cases were treated surgically. Our surgical rate after failed methotrexate treatment was 6.8% (24/348). A single dose of methotrexate was administered to two patients who underwent laparoscopic salpingotomy because there was no drop in β-hCG values.

## V. DISCUSSION

Although most cases are recognised and treated appropriately, women still die as a result of late diagnosis and suboptimal management of ectopic pregnancy. Combination of ultrasonographic findings, consecutive levels of human chorionic gonadotrophin and also clinical suspicion are important for diagnosis. In a study by Condous et al [9] demonstrated that an experienced sonologist can diagnose 75-80% of ectopic gestation by transvaginal sonography in the first visit itself. In our study the diagnosis of each patient was confirmed with USG and serial  $\beta$ hCG measurements. In our study 344 (97.2.5) echographically visible tubal pregnancies were diagnosed by ultrasonography. Moreover USG assessments were found to be compatible with EP diagnosis.

Although EP prevalence among women admitting to emergency services with bleeding in first trimester, abdominal or pelvic pain ranges from 6-16%, the incidence of EP differs between studies [10]. In a recent study from Bangladesh by Yeasmin et al [11] the incidence of EP was reported to be 7.4/1000 deliveries with a majority of patients belonged to the age group 20-25 years (44.6%). Contrary to current literature, because of being done in rural areas (inflammation, smoking, infection), having higher cesarean rates compared to the others and being tertiary referral center our study found an actual EP incidence of 7.6%. A history of ectopic pregnancy was noted for 8% of our patients, was not close to the range of 12.6% to 14% reported in most recent studies [12], [13-15]. The reason for our study to be lower than previous studies was that salpingectomy rate was higher in our study compared to these studies.

Interstitial pregnancy is a rare type of ectopic pregnancy that accounts for 2-4% of all ectopic pregnancies and almost 20% of all deaths caused by ectopic pregnancy [16]. Similar to the literature, we found the interstitial pregnancy rate 2.1% (10/374). Although the site of the bleeding was clamped, and cornual resection with the conception products inside was done immediately, a death was observed.

Fourteen cervical EPs were diagnosed and treated with half of the methotrexate to the pouch in 50mg/m<sup>2</sup> and the remaining half as the intramuscular, with additional local potassium chloride (KCl) in the presence of fetal cardiac activity, reported an overall success rate of 78.5%; in three cases these treatment modality were failure, all failures had fetal cardiac activity and in all three sudden bleeding cases, dilation and curettage was followed by balloon tamponade and the cervix was sutured all around.

Followed by tubal localization, cesarean section scar ectopic pregnancy rate was second with 3.8%. A total of 18 cesarean scar pregnancies were detected in this study. We applied half of the methotrexate to the pouch in 50mg/m<sup>2</sup> and the remaining half as the intramuscular. Although we had a fetal heartbeat in two of the cases, we had a hundred percent success in treatment.

We have obtained from our data that the ectopic pregnancy in patients whose  $\beta$ -hCG are persists under 1000 iu for more than 3 weeks is ruptured and transformed into an organized hematoma. So if expectant management is done and  $\beta$ -hCG persists under 1000iu for more than 3 weeks, it is beneficial to apply a surgical procedure. In the majority of cases of recurrent ectopic pregnancy, our data revealed that methotrexate treatment was successful even if  $\beta$ -hCG was above 5000 iu if fetal cardiac activity was absent. Although Liscomb et al reported that a history of previous ectopic pregnancy appears to be an independent risk factor for failure of systemic methotrexate treatment, we found systemic methotrexate treatment failure in nine (23.6%) of 38 of previous ectopic patients and this does not coincide with what they find, but same as them we found that

failure is not affected by previous treatment method [17]. We explain this high success rate with early referral to our clinic due to the fact that patients have ectopic pregnancy experiences; but we think that this result is not significant because of the small number of patients with recurrent ectopic pregnancy in our study.

In the present study, tubal pregnancy found in 88.6% EP patients. Deeba et al. [18] found that other EP sites are uncommon with an incidence of 0.6% and localized in ovaries, cervix and abdomen. This contradicts our conclusions, because in our study, previous cesarean and curettage rates, ie risk factors for ectopic pregnancy, were found to be higher than in these studies.

A single methotrexate injection was sufficient for 90.2% of our patients, and a second injection resolved 55.5% of the remaining cases. A methotrexate single-dose protocol successfully treated 78.5% of the 400 cases of ectopic pregnancy included in a study done by Bonin et al. [19]. We believe that the high success rate of single-dose methotrexate treatment in our cases is due to the appropriate relevance at the outset. Bonin et al. [19] found that ectopic pregnancy rate was 8.5% despite the contraception, in their study. This result contradicts our study. In our study, we found the ectopic pregnancy rate 43% despite the contraception and we attribute this to the inappropriate use of contraceptive methods and co-factors that pose a risk for ectopic pregnancy.

The pretreatment  $\beta$ -hCG level is a known predictor of success for methotrexate treatment, but thresholds reported in the literature vary from 1000 IU/L to as much as 5000 IU/L. In our study, initial  $\beta$ -hCG values below 1500 IU/L were associated with a success rate of 86%. Our threshold value of 1500 IU/L was the same or similar to those retained by several other teams. For example, both Nazac et al. [13] retained the 1000 IU/L threshold and Krissi et al. retained 1300 IU/L for their 2011 study [20]. We also noticed that as the size of echographically visible lateral extrauterine masses increased so did failure rates, but this association was not statistically significant. This same dynamic has been reported in most studies [21].

We found medical treatment such as local or systemic injection of methotrexate success rates 93.2 %. Therefore, we think that methotrexate injection should be used as the first option in appropriate cases. The main power of the study is the size of the patient series, one of the greatest to date. The main limit of our study is that it is retrospective: although it reflects our clinical practice experience, our study could be affected by certain biases and limits innate to this type of study.

## VI. CONCLUSION

In conclusion early and accurate diagnosis and termination constitute main points of the management. Based on individual patient factors conservative, medical and surgical treatment options should be considered. Moreover improving fertility outcomes depends on appropriate medical or surgical treatment.

## VII. CONFLICT OF INTEREST

The author declares that there is no conflict of interest

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