

## Changing Trend of Tubal Ectopic Pregnancy Management During the Experience of Seven Years

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**ABSTRACT Objective:** Ectopic pregnancy is a condition where a fertilized egg gets implanted outside the uterus. The most common site of attachment is the fallopian tube and the condition is termed tubal ectopic pregnancy. It is considered a gynecologic emergency if it is neglected or overlooked. Technological progress and advances in management modalities have provided clinicians with various treatment options for tubal ectopic pregnancy. In the current study, we analyzed the management trends in tubal ectopic pregnancy including an evaluation of the clinical profile and management modalities of the cases. **Material and Methods:** The present study is a retrospective observational study that included women with tubal ectopic pregnancy who were admitted to the department of obstetrics and gynecology. The patients were allocated to two groups, namely MTX, and surgical treatment groups. **Results:** Of the 207 women included in the study, 84 and 123 were treated with surgery and MTX, respectively, at the first admission. The most common symptom noted was lower abdominal pain in 182 (87.9%) patients and vaginal bleeding was present in 171 (82%) women. The most common ultrasonographic finding was adnexal mass in 156 (75%) women. We performed salpingectomy in 67 (56%) and salpingostomy in 52 (44%) cases that were finally surgically treated ( $n=119$ ). Our trend analysis reported a significant and quadratic increasing trend for salpingectomy ( $\chi^2=5.539$ , degrees of freedom [ $df$ ]=1,  $p=0.02$ ) from 2009 to 2015. There was a significantly increasing linear trend in the MTX treatment group, whereas the surgery group presented a significant decreasing linear trend ( $\chi^2=18.56$ ,  $df=1$ ,  $p=0.001$ ). **Conclusion:** The present study observed a downward change in the management strategies of tubal ectopic pregnancy for surgery and an upward change for medical management of cases with MTX between 2009 and 2015.

**Keywords:** Methotrexate; salpingectomy; salpingostomy; surgery; tubal ectopic pregnancy

Ectopic pregnancy is defined as the implantation of a fertilized ovum outside the uterine cavity, most common site being the fallopian tube. The incidence of ectopic pregnancy varies between 1% and 2% in the general population, with an estimated 11,000 ectopic pregnancies diagnosed each year.<sup>1-3</sup> It is responsible for 3% to 4% of pregnancy-related deaths.<sup>4,5</sup>

A study reported at least 90% of all ectopic pregnancies to occur in the fallopian tube, known as tubal ectopic pregnancy.<sup>6</sup> Tubal ectopic pregnancy is managed surgically via an open or laparoscopic route with salpingectomy or salpingostomy. Salpingectomy has a high success rate and is the preferred treatment modality for a ruptured tubal ectopic pregnancy. It is also effective in patients who are hemodynamically unstable because of uncontrolled bleeding from the ectopic focus. Conservative surgery via salpingostomy is a suitable approach for women whose tubal integrity remains intact.<sup>7,8</sup>

Various nonsurgical strategies have also been employed for treating ectopic pregnancy including medical treatment and expectant management.

Expectant management is offered to asymptomatic patients with very low and decreasing levels of human chorionic gonadotropin ( $\beta$ -hCG).<sup>9</sup> Medical management of tubal ectopic pregnancy commonly involves systemic or local administration of methotrexate (MTX). It is available for patients who are hemodynamically stable with no evidence of acute intra-abdominal bleeding and no contraindication to MTX therapy. Serial quantitative measurement of  $\beta$ -hCG is mandatory to monitor the treatment and following the complete resolution of trophoblastic tissue.<sup>10</sup>

The first successfully treated ectopic pregnancy was managed by removing the tube and was reported toward the end of the 19th century. On the other hand, medical treatment with systemic administration of MTX has evolved as a management strategy for ectopic pregnancy since the second half of the 20th century.<sup>11,12</sup> From then until today, the management of ectopic pregnancy has experienced a revolution. The availability of a variety of management strategies provides the medical professionals several options to choose from before patient's condition deteriorates and tubal integrity is lost. Each strategy is implemented taking into consideration the condition of the facility, skills or experiences of the medical professionals, and patient's preferences. Moreover, owing to these conditions, management strategies for the treatment of ectopic pregnancy and attitude of the clinicians toward treatment options have changed over decades.<sup>13-15</sup>

In the present study, we primarily focused on the trends of tubal ectopic pregnancy management with surgery and single-dose systemic MTX treatment in our clinical practice. Our secondary objectives were to evaluate clinical profiles of women with tubal ectopic pregnancy.

## MATERIAL AND METHODS

We performed a single-center retrospective observational study on women with ectopic pregnancy admitted to the department of obstetrics and gynecology of the Istanbul Medeniyet University, Göztepe Teaching and Research Hospital, Istanbul, Turkey, between January 2009 and December 2015.

All data were obtained from patient medical files and the hospital pharmacy registry. Local Ethics Committee approval was obtained for this study.

All patients in the dataset were treated as inpatients. Inclusion criteria for the study included diagnosis of ectopic pregnancy and localization in tuba uterina. Exclusion criteria were defined as cervical, ovarian, cornual, or cesarean scar ectopic pregnancy.

The diagnosis of ectopic pregnancy was based on direct transvaginal ultrasound signs (an adnexal mass, extrauterine gestational sac with or without a yolk sac, and/or embryonic pole with or without cardiac activity in the presence of an empty uterus) and also with unsuitable  $\beta$ -hCG kinetics for a viable pregnancy (no doubling, little reduction in or stagnation of levels at 48 h). All patients were evaluated with laboratory tests, including serum  $\beta$ -hCG concentration, complete blood count, and liver and renal function tests, and were administered anti-D prophylaxis intramuscularly if they were Rhesus negative and their partners were Rhesus positive. Ectopic pregnancies were managed either via medical treatment with single-dose MTX or surgically with salpingostomy or salpingectomy performed via laparoscopy or laparotomy. No patient was managed expectantly because this management method was not preferred as per our clinical management policy for ectopic pregnancy.

The patients were divided into two treatment groups based on the treatment method performed at the first presentation: MTX group ( $n=88$ ) and surgical treatment group ( $n=119$ ). Surgical treatment was further classified into surgery as the first-line treatment at the initial presentation ( $n=84$ ) and surgery as the second-line treatment in patients who failed in MTX treatment ( $n=35$ ). Also, surgical treatment types were classified into surgery with salpingectomy ( $n=67$ ) and surgery with salpingostomy ( $n=52$ ). Medical management consisted of a single shot of MTX (50 mg/m<sup>2</sup> body surface area) intramuscularly with monitoring of  $\beta$ -hCG levels on days 4 and 7 and following serial measurement of quantitative  $\beta$ -hCG weekly until a value of < 5 IU/L was reached. Demographic and clinical data, including age, gestational age, gravidity, parity, laboratory values

( $\beta$ -hCG level and hematocrit), and transvaginal ultrasound findings of the ectopic pregnancy (mass size, presence or absence of cardiac activity [CA] of the embryo [Embryo CA (+) or Embryo CA (-)]) at admission, were obtained from records.

The trend analyses of management methods and surgery with salpingectomy or salpingostomy were performed for the interval from 2009 to 2015. Since a significant change occurred in the management strategies in 2012, the 7-year study period was divided into two time periods based on the cut-off year (2012). All cases treated with MTX and surgery at the first presentation were allocated into two groups, that is, before 2012 and after 2012. The clinical and demographic properties of each treatment method were compared between the two time periods.

## STATISTICAL ANALYSIS

Statistical analyses were performed using the SPSS 15.0 and R statistical software.<sup>16</sup> All data were reviewed for outliers, missing data, and normality assumptions. The differences in group proportions were analyzed using  $\chi^2$  test for independence variables. Fisher's exact test was used when more than 20% of cells had expected counts of <5, via the SPSS cross-tables module. The differences between the medians were analyzed using the Mann-Whitney *U* test, as the distributions were skewed. The results were reported as median (interquartile ratio [IQR]) and minimum and maximum for quantitative variables and as percentages for categorical variables. The different trends in the treatment strategies and surgical treatment methods (salpingectomy and salpingostomy) were analyzed using  $\chi^2$  trend test in R statistical software. The cut-off year where a significant change occurred in management strategies was checked using the proportion test.

## RESULTS

The present study included 207 patients with tubal ectopic pregnancy between 2009 and 2015. Of these, 119 underwent surgery (84 as first-line treatment and 35 secondary to MTX failure). Salpingectomy and salpingostomy were conducted in 67 (56%) and 52 (44%) cases treated with surgery,

respectively. A hundred twenty-three patients were treated with MTX as the first-treatment; 88 of them (71.5 %) were treated successfully.

Figure 1 shows a significant increasing linear trend in the MTX treatment group and a significant decreasing linear trend in the surgery group ( $\chi^2 = 18.56$ , degrees of freedom [df]=1,  $p < 0.001$ ). The trend analysis of surgery types, namely salpingectomy and salpingostomy, is presented in Figure 2. There was a significant quadratic increasing trend for salpingectomy ( $\chi^2=5.539$ ,  $df=1$ ,  $p=0.02$ ; (Figure 2).

Table 1 presents clinical symptoms and transvaginal ultrasonography findings of women with tubal ectopic pregnancy. The most common presentation symptom was lower abdominal pain in 87.9% (182/207) patients. The most common ultrasonographic finding was ectopic adnexal mass in 75% (156/207) patients. Table 2 lists demographic and laboratory features and hospitalization data of women with tubal ectopic pregnancy. The hospitalization duration decreased significantly from 2009 to 2015. However, other variables did not show any change in the 7-year period.

We established two time periods based on the year 2012 as the first period: the triennial period from 2009 to 2012 and the second period, the quadrennial period from 2012 to 2015. The cases treated with MTX in the second period had significantly higher serum  $\beta$ -hCG levels and mass size than those treated during the first period. The clinical and laboratory findings of each treatment group were compared between the first and second periods and are presented in (Table 3).

## DISCUSSION

Ectopic pregnancy commonly presents with lower abdominal pain and vaginal bleeding during 6th to 10th gestational weeks.<sup>17,18</sup> In the present study, 88% of cases were admitted with a complaint of lower abdominal pain, of which 82% reported vaginal bleeding.

Currently, unruptured ectopic pregnancy, that is, with an intact uterus, is diagnosed using a combination of transvaginal ultrasonography and

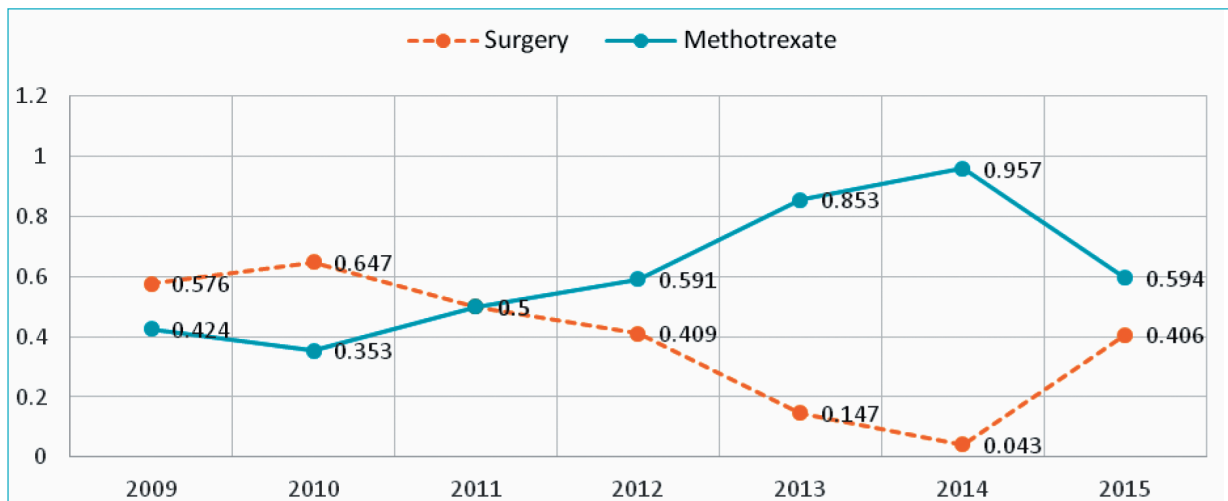


FIGURE 1: Trend of the treatment strategies of tubal ectopic pregnancy.

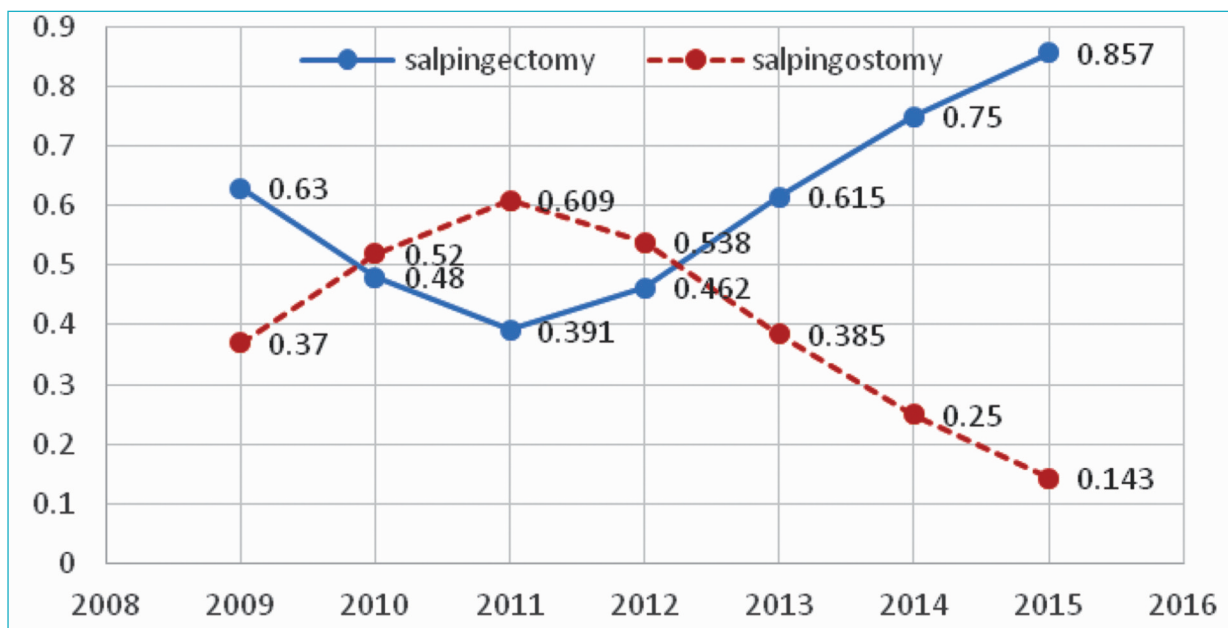


FIGURE 2: Trend of the surgery with salpingectomy and salpingostomy.

serial measurement of serum  $\beta$ -hCG levels. An adnexal mass in the presence of an empty uterus is reported to be the most common ultrasonographic finding in around 60% cases of tubal ectopic pregnancy.<sup>18</sup> Another study reports empty extrauterine gestational sac to be observed in around 20% of cases.<sup>19</sup> Approximately 7.3% of the ectopic pregnancy cases have an embryonic pole with CA.<sup>20</sup> The ultrasonographic examination describes hemoperitoneum as the presence of free fluid imaging in the pouch of Douglas and has been reported

in 28% to 56% cases of ectopic pregnancy. This finding commonly occurs by leakage of blood from the fimbrial tube.<sup>21</sup> Disseminated free fluid in abdominal cavity or hemoperitoneum is an important marker of serious intra-abdominal bleeding and should be considered in cases of ruptured tubal ectopic pregnancy.<sup>22</sup>

The present study confirmed the previous characteristic findings of ectopic pregnancy by transvaginal sonography. An inhomogeneous ad-

**TABLE 1:** Clinical symptoms and transvaginal ultrasonography findings of women with tubal ectopic pregnancy.

Year	Vaginal bleeding n (%)	Lower abdominal pain n (%)	Ultrasound findings of tubal ectopic pregnancy cases				
			Free fluid confined to pelvis n (%)	Free fluid extended to abdomen n (%)	GS in the ectopic-mass n (%)	Ectopic Mass n (%)	Embryo with cardiac activity (+) n (%)
2009 (n=33)	28 (84)	29 (89)	22 (67)	2 (6)	7 (21)	26 (78)	1 (7.1)
2010 (n=34)	26 (76)	28 (82)	24 (71)	7 (21)	7 (21)	27 (79)	0 (0)
2011 (n=34)	30 (88)	29 (85)	26 (77)	5 (15)	3 (9)	25 (73)	0 (0)
2012 (n=22)	16 (72)	19 (86)	10 (46)	3 (14)	3 (14)	17 (77)	1 (7.7)
2013 (n=34)	30 (88)	32 (94)	16 (47)	1 (3)	9 (27)	24 (70)	6 (21)
2014 (n=23)	17 (74)	19 (83)	9 (39)	0	1 (4)	16 (69)	1 (4.5)
2015 (n=27)	24 (88)	26 (96)	17 (63)	6 (22)	3 (11)	21 (77)	2 (12.5)
Total (n=207)	171 (82)	182 (87.9)	124 (59.9)	24 (11.6)	33 (16)	156 (75)	11 (5.3)

GS: Gestational Sac.

**TABLE 2:** Demographic and clinical characteristics of the tubal ectopic pregnancy treated with single-dose methotrexate and surgery.

	Age (year)		Gravidity (n)		Parity (n)		Gestational age (week)		Hematocrit (%)		β-hCG (IU/L)		Hospitalization day	
Pa	0.860		0.25		0.625		0.118		0.12		0.150		<0.001	
Year	Median (IQR)	Min; max	Median (IQR)	Min; max	Median (IQR)	Min; max	Median (IQR)	Min; max	Median (IQR)	Min; max	Median (IQR)	Min; max	Median (IQR)	Min; max
2009 (n=33)	30 (5.25)	19;34	6 (1)	5;8	2 (2)	0;4	4 (2)	5;6	35 (6.5)	22;42	1561 (2613)	140.;7807	5 (7)	2;26
2010 (n=34)	26.5 (10.5)	23;38	6 (2.7)	5;10	1 (2)	0;4	4 (2)	5;6	35 (5)	27;39	1662 (1704)	278;5274	4 (4)	1;16
2011 (n=34)	29 (7)	24;40	5 (1)	4;8	1 (2)	0;5	3 (2)	5;7	34 (7)	19;40	978 (1850)	325;8900	6 (6)	2;13
2012 (n=22)	27 (13.5)	20;43	6 (2.5)	5;8	2 (1.2)	0;5	3 (2)	5;8	33.5 (4.7)	24;41	2544 (3274)	106;8307	2 (1)	1;10
2013 (n=34)	30 (9.5)	20;45	6 (1)	5;8	1 (2)	0;3	4 (2)	5;6	35 (4.5)	23;41	8307 (6974)	395;15554	2 (1.2)	1;10
2014 (n=23)	30 (10.5)	23;41	6 (1)	5;7	1 (1)	0;3	4 (2)	5;8	37 (4)	24;43	1576 (6989)	229.;21452	1 (3)	1;11
2015 (n=27)	31 (9)	23;41	6 (1)	5;7	1 (2)	0;4	3 (2)	5;7	33 (2)	30;41	2707 (3520)	516;20925	2 (2)	1;5

IQR: Interquartile range; Min; max: Minimum; maximum; β-hCG: Human chorionic gonadotropin; a: P value calculated using X2 test of independence.

nexal mass was the most common ultrasonographic finding (75%). A gestational sac and an embryonic pole with positive cardiac activity were visualized in the 16% and 5.3% of cases, respectively. The free pelvic fluid was reported in 59.9% of cases.

We evaluated the trends in methods of treatment used in patients with tubal ectopic pregnancy at our clinic practice. On analysis, we found that surgery demonstrated a decreasing trend (57.6% for 2009 and 40.6% for 2015), whereas MTX treatment was associated with an increasing trend (42.4 and

59.4%, respectively, for 2009 and 2015). A previous trend analysis of ectopic pregnancy management reported a significant decrease in cases treated with surgery (from 85.5% in 2006 to 72.7% by 2015); however, the study reported a significant increase in the MTX treatment (from 14.5 to 27.3%, respectively, from 2009 to 2015).<sup>13</sup> Another study reported an increase from 11.1% in 2002 to 35.1% in 2007 in the rate of ectopic pregnancies treated with MTX, whereas the surgical management rate decreased over the study period from 88.9% to 64.9%.<sup>12</sup> The



**TABLE 3:** At the first admission, clinical and laboratory characteristics of the treatment groups in the two periods between 2009 and 2015 years.

At the admission	MTX Treatment Group N:123					Surgical Treatment Group N:84				
	Before 2012 N:43		2012 and after N:80		P value	Before 2012 N: 58		2012 and after N:26		P value
	Median (IQR)	Min; max	Median (IQR)	Min; max		Median (IQR)	Min; max	Median (IQR)	Min; max	
Age (year)	29 (7)	19; 40	30 (10.7)	20; 45	0.61 <sup>a</sup>	31.5 (10.2)	20;45	30.5 (6.2)	25;42	0.479 <sup>a</sup>
Gravidity (n)	3 (3)	1;6	3 (3)	1;8	0.81 <sup>a</sup>	3 (3)	1;7	3 (3)	1;8	0.079 <sup>a</sup>
β-hCG (IU/L)	1594 (2086)	140; 8900	2356 (5989)	106; 21452	0.003 <sup>a</sup>	2203 (5716)	176; 55023	3430 (9527)	156; 29841	0.208 <sup>a</sup>
Mass size (mm)	20 (9)	0;40	17.5 (13)	0;60	0.05 <sup>a</sup>	30 (25)	10;66	30 (13.7)	17;50	0.996 <sup>a</sup>
Gestational age (week)	6 (2)	4;10	6 (1)	5;8	0.32 <sup>a</sup>	6 (1.2)	4;12	6 (1.2)	4;8	0.209 <sup>a</sup>
Hematocrit (%)	1 (2.3)	26;40		24;43	0.91 <sup>a</sup>	34 (7)	19;42	32.5 (5.5)	23;41	0.285 <sup>a</sup>
ECA (+) N (%)	1 (2.3)		10 (12.5)		0.95 <sup>a</sup>	9 (15.5)		3 (11.5)		0.7 <sup>b</sup>

a: P-value calculated using the Mann-Whitney U test; b: P-value calculated using a  $\chi^2$  test

study by Trabert et al.<sup>14</sup> reported a significant decrease in surgical treatment from 48.1% to 30.7% in the management of ectopic pregnancy over a 20-year period from 1993 to 2007. Overall, these analyses imply a shift in the rate from surgery to MTX treatment for ectopic pregnancy, from 12.8% to 24% in different time intervals. In the current study, this rate was 17%, within the range reported by other researchers. Further, the present study included only cases of tubal ectopic pregnancy, whereas other studies were conducted based on ectopic pregnancies in general without consideration for localization. However, this inequality is negligible because tubal ectopic pregnancies constitute the majority of ectopic pregnancy cases.

Salpingostomy or salpingectomy is a feasible surgical intervention for tubal ectopic pregnancy with a similar effect on the direct medical cost of treatment and fertility prospect in women with a healthy contralateral tube.<sup>23</sup> Single-dose MTX administration and a close follow-up with serial β-hCG measurement could be necessary owing to the probability of persistent trophoblastic tissue.<sup>24</sup> Decreasing trends in surgical intervention with salpingostomy have been reported.<sup>14</sup> A similar decreasing trend was reported from 37% in 2009 to 14.3% in 2015 in the present study in the salpingostomy rate among patients with tubal ectopic pregnancy treated surgically. On the other hand, salpingectomy demonstrated a significant quadratic increasing trend (63% and 85.7%, respectively).

The diagnosis of ectopic pregnancy has led to various management strategies that are preferred considering hemodynamic symptoms, serum β-hCG levels, ultrasound scan findings (the presence of embryonic CA and ectopic mass size) as well as patient's preference and hospital facilities.<sup>25</sup>

We evaluated the β-hCG levels and ultrasound scan findings for MTX treatment between two time periods (from 2009 to 2012 and 2012 to 2015). We found the median β-hCG level to be 1,594 IU/L in the first period and 2,356 IU/L in the second period. The differences in β-hCG level between the two time periods were significant. The guidelines of the American Society for Reproductive Medicine committee (2006 and 2013) proffer the highest β-hCG level for MTX treatment to be 5,000 IU/L.<sup>26,27</sup> A national guideline of the Royal College of Obstetricians and Gynecologists (RCOG, 2010) has suggested that the β-hCG level for MTX treatment should be below 3,000 IU/L.<sup>28</sup> The present study reported a lower median β-hCG level in the two periods than the threshold levels of β-hCG levels. Especially, the β-hCG value in the first period showed an evident difference from these thresholds.

In the surgery group, the median β-hCG level was 2,203 IU/L in the first period and 3,430 IU/L in the second period. These values were again considerably lower compared to the 5,000 IU/L β-hCG level. However, a consistency between the β-hCG level in the second period and the threshold β-hCG level suggested by RCOG (2010) existed.<sup>28</sup>

Nearly all guidelines consider a mass size of 35 mm diameter to affect management and the presence of embryonic CA as a contraindication for MTX treatment. In the present study, the median ectopic mass size of the two management groups in both periods was smaller than 35 mm in diameter. In the MTX treatment group, the number of women with embryonic cardiac activity (ECA (+)) was 11, 1 in the first period and 10 in the second period.

A comparison of results obtained from this study and suggestions of the guidelines evidently revealed the clinicians' cautionary attitude toward MTX treatment and the favorable attitude toward surgery in the first period. Clinical practice guidelines assist the physicians in clinical decision making. However, changing the general attitude toward any treatment requires considerable time when the clinicians gain clinical experience with the guideline suggestions.<sup>29</sup>

Historically, surgery has been the first method in the diagnosis and treatment of ectopic pregnancy and has been performed as part of clinical practice for decades.<sup>30</sup> It has been succeeded by medical management with MTX that has undergone an adaptation period. Besides its familiarity and practical experience, surgical management has several advantages, such as providing rapid confirmation of the diagnosis and shortening resolution and monitoring times.

Currently, MTX treatment for tubal ectopic pregnancy is widely recognized<sup>17</sup>; however, it requires an adaptation period. The regular quantification of  $\beta$ -hCG levels is mandatory with treatment with MTX, and average follow-up varies from 26.5 to 32 days.<sup>31,32</sup> During this period, almost 75% of women have experienced abdominal pain, termed as "separation pain."<sup>33</sup> Also, the risk of tubal rupture has occurred at a rate of 7% to 14% during the follow-up period.<sup>34-36</sup> Therefore, it is necessary to distinguish between separation pain and abdominal pain caused by a ruptured ectopic pregnancy during the follow-up period, because the risk associated with a hemodynamically unstable patient during the follow-up period could result in an extension of the adaptation period for clinicians.

The study population in the present study was based on a single center that allowed us to evaluate

the trend from 2009 to 2015, considering that the surgical equipment, diagnostic facilities, and accessibility to these procedures have remained nearly constant. We hypothesized that clinicians' attitude toward ectopic pregnancy management changed with their experience and due to positive outcomes with MTX treatment. The increase in maximum  $\beta$ -hCG level and even preference of MTX as the first-line of treatment in the presence of embryonic CA in the MTX group during the second period supports our hypothesis. Clinicians' attitude toward any management strategy is affected by many factors, such as their individual properties, their hospitals having suitable and accessible diagnostic and therapeutic tools, and patients' attitude toward treatment modalities. Using a prospective study design ensures that accurate information is obtained about clinicians' attitude toward management strategies for ectopic pregnancy and the variables affecting it and affected by it.

In conclusion, the present study demonstrated an increasing trend in treatment with MTX and a decreasing trend in surgical treatment between 2009 and 2015 for the management of tubal ectopic pregnancy.

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#### **Conflict of Interest**

*No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.*

#### **Authorship Contributions**

**Idea/Concept:** Halenur Bozdağ; **Design:** Halenur Bozdağ; **Control/Supervision:** Esra Akdeniz; **Data Collection and/or Processing:** Ömer Gökhan Eyisoy; **Analysis and/or Interpretation:** Esra Akdeniz, Halenur Bozdağ; **Literature Review:** Halenur Bozdağ, Esra Akdeniz, Ömer Gökhan Eyisoy; **Writing The Article:** Halenur Bozdağ, Esra Akdeniz; **Critical Review:** Halenur Bozda.

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