

The Retrospective Analysis of Factors Determining the Success of Single-Dose Methotrexate Treatment in Ectopic Pregnancy

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ABSTRACT

Objective: We aimed to investigate treatment outcomes, treatment failure rates, factors causing failure, and complications of treatment in patients followed up with ectopic pregnancy and receiving methotrexate (MTX) treatment.

Materials and methods: All ectopic pregnancies in a tertiary perinatology center who had single dose MTX between January 2015 and January 2021 were retrospectively included in this study. The demographic data of the women (age, gravida, parity, abortus numbers) and delivery [normal and cesarean section (C/S)] types were analyzed. The size of the mass, β -hCG level, presence of intra-abdominal free fluid and USG findings were recorded. The effectiveness of the treatment and the need for surgical treatment after MTX treatment were also investigated.

Results: Overall, 93 ectopic pregnancies who had single dose MTX treatment were included in this study. The mean age was 30.4 years (SD \pm 5.2). Previous ectopic pregnancy rate was 9.9% and 13.6% had free fluid in the abdomen. More than one third (35.8%) had undergone previous surgery and 8.6% had chronic disease. The median β -hCG level was 1763 mIU/ml (minimum 129 – maximum 67854, IQR 1010 - 2723 mIU/ml). The mean size of the mass was 9.3 mm (SD \pm 6.1). A single dose of MTX treatment was found to be effective in 51.9%. β -hCG levels at the time of admission, mass size, patients age and pregnancy week were not effective on the success of single-dose MTX treatment.

Conclusion: Single dose MTX therapy is used effectively and safely in the first treatment of ectopic pregnancy.

KEYWORDS: Ectopic pregnancy, methotrexate, single dose treatment

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INTRODUCTION

Although the frequency of ectopic pregnancies has increased gradually in recent years, ectopic pregnancies constitute 1-2% of all pregnancies [1]. Ectopic pregnancies are still the important etiologies of maternal losses in the first trimester [2]. With the development of modern medicine, early diagnosis of ectopic pregnancies has become commonplace, and using the medical treatment has become widespread. Low cost, low anesthesia and surgical complications and low morbidity make medical treatment superior [3].

The most commonly used medical treatment agent as an alternative to surgical treatment is methotrexate (MTX) [3, 4]. It has low side effects and high efficiency [3]. Serum β -hCG level at diagnosis, size of ectopic pregnancy, fetal heart activity and presence of yolk sac are reported as factors

affecting the treatment success [5, 6, 7]. In addition, a single-dose of MTX treatment (SDMT) is preferred first in ectopic pregnancies [8]. A SDMT is administered because it has a similar resolution rate with multiple doses, has fewer side effects, requires less follow-up, is cheaper, and has a success rate of 88% [8].

We aimed to investigate treatment outcomes, treatment failure rates, factors causing failure, and complications of treatment in patients followed up with ectopic pregnancy and receiving SDMT.

MATERIALS AND METHODS

Patients' selection

All ectopic pregnancies between 18-42 years during the January 2015 and January 2021 period were retrospectively

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included in this study. Patients who had multiple MTX doses and operated for acute abdomen pathologies were excluded from this study. Ethics committee approval was given by the Demiroglu Bilim University medical faculty scientific research ethics committee (Date: 2021, No: 2021-195). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Data Collection and Assessment of Patients

The demographics (age, gravida, parity, abortus numbers), complaints and delivery [normal and cesarean section (C/S)] types were analyzed. The size of the mass, beta human chorionic gonadotropin (β -hCG) level, intra-abdominal free fluid in the pelvis (FFIP) and USG findings were recorded. The treatment effectiveness was also investigated.

Statistical analysis

Data were analyzed using the SPSS 25.0 (IBM, Armonk, NY: IBM Corp.) program. Continuous variables were expressed as mean \pm standard deviation, median (interquartile range, IQR), and categorical variables as numbers (n) and percentages (%). Student's t-test and Mann-Whitney U test were used to compare differences between independent groups. The Chi-square or Fisher's exact probability tests were used to compare demographics. In all analyses, $p < 0.05$ was considered statistically significant.

RESULTS

Overall 93 ectopic pregnancies were analyzed. Twelve women were excluded for missing data and had concomitant acute abdominal pathology. The mean age of the 81 patients was 30.4 years (SD \pm 5.2) (Table 1). The median number of gravida was 3 (minimum 1 – maximum 8, IQR 2-4), and the median parity number was 1 (minimum 0 – maximum 5, IQR 1-2). While 65.4% (n=53) had ≥ 1 abortion history; 12.3% had no history of abortion (Table 1).

One-third (35.8%) of women had a previous C/S surgery (Table 1). The frequency of previous ectopic pregnancy was 9.9% (n=8) (Table 2). In addition, while 13.6% (n=11) of the patients had FFIP; more than one third (35.8%) had undergone previous surgery and 8.6% (n=7) had chronic disease (Table 2). The median gestational week was 6⁺⁴ (minimum 2⁺³ - maximum 17⁺⁴, IQR 4⁺³ - 7⁺⁵ weeks) (Table 1). Vaginal bleeding and abdominal/groin pain were in 32.1% (n=26) and 23.5% (n=19). The median β -hCG level was 1763 mIU/ml (minimum 129 – maximum 67854, IQR 1010 - 2723 mIU/ml) (Table 3). The mean size of the mass was 9.3 mm (SD \pm 6.1) (Table 3). A SDMT was effective in 51.9% (n=42) of the patients; After the treatment, 48.1% of the patients had medical treatment failure and underwent surgery operation (Table 3). No significant difference was observed between the β -hCG levels, mass size, FFIP and treatment effectiveness ($p=0.152$, $p=0.881$ and $p=0.457$, respectively) (Table 4). In addition, patient age and gestational week had no any affect

on the efficacy of SDMT ($p=0.275$ and $p=0.140$, respectively) (Table 4).

DISCUSSION

MTX used in medical treatment is as safe as it is effective in ectopic pregnancies [9]. Despite this, the success of medical treatment is still not complete; however, the prognostic factors that affect the success of SDMT are controversial. We investigated the efficacy of SDMT in ectopic pregnancy.

Ectopic pregnancy is more common with increasing age in women [10, 11]. Nybo AA et al. [10] showed the frequency of ectopic pregnancy was 1.4% in women aged 21 years and 6.9% in women aged 44 years. We found the mean age was 30.4 years. While the ectopic pregnancy rate cannot be given according to the age range; supporting the literature, the age group was > 30 years.

Women's gravida, parity, abortion and gestational week at presentation have no effect on the occurrence of ectopic pregnancy [12]. Gravida, parity numbers and the median gestational week in women with ectopic pregnancy were 3, 1 and 6⁺⁴, respectively. Since women without ectopic pregnancy were not included, the effect of gravida, parity, abortion numbers and gestational week on ectopic pregnancy could not be evaluated. The most common complaint in ectopic pregnancy is abdominal pain [13]. Also, Pal A et al. [14] reported to abdominal pain (91.7%) and vaginal bleeding (71.7%) as most complaints similar with our results. Celik E et al. [15] showed the presence of endometrial thickness and FFIP did not affect the success of SDMT; however the negative correlation between mass size and the success of SDMT. Also, the FFIP and mass size do not affect the success of SDMT in ectopic pregnancies [5, 11]. Similar with literature, mass size and FFIP did not affect the success of SDMT. We showed the mass size and FFIP are not risk factors for the SDMT success.

There are studies reporting that success rates decrease as the pre-treatment β -hCG level increases in ectopic pregnancies [15, 16]. β -hCG levels before the treatment of ectopic pregnancies could be used as a marker showing whether a SDMT would be successful [17, 18]. On the other hand, Celik E et al. [15] from our country reported that β -hCG levels were not effective on the treatment success. We showed that β -hCG levels at the time of admission were not effective on the success of SDMT. The success rates of SDMT are between 64.0% and 94.2% [19-22]. We determined the success rate of SDMT was 51.9%. This rate is lower than the literature. This study was conducted in a tertiary center, more complicated and difficult cases were referred to this center and it explain the lower success rate of SDMT. Limitations of this study; (1) being a single-center study and the small patient group constitute important limitations in the generalization of our results; (2) ectopic pregnancy patients as well as healthy pregnancies in the same age group as the control group should not be included.

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CONCLUSION

SDMT is used effectively and safely in the first treatment of ectopic pregnancy. Although gestational week, age, mass size and β -hCG levels have been reported to affect the success of treatment, the effectiveness varies depending on the patient and department features. Therefore, further studies are needed for potential prognostic factors.

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Table 1. Demographic characteristics of patients with ectopic pregnancy.

Age (year) [mean (\pmSD)]	30.4 (\pm 5.2)
Gestational week (year) [median (min-max)]	6 ⁺⁴ (2 ⁺³ -17 ⁺⁴)
Gravida (n) [median (min-max, IQR)]	3 (1-8, 2-4)
Parity (n) [median (min-max, IQR)]	1 (0-5, 1-2)
Abortus [n (%)]	
0	10 (12.3)
1	53 (65.4)
≥ 2	18 (22.2)
Delivery type [n (%)]	
NSVD	52 (64.2)
C/S	29 (35.8)

C/S: cesarean sectio, IQR: interquartile range, min: minimum, max: maximum, NSVD: normal spontaneous vaginal delivery, SD: standart deviation

Table 2. Previous surgery and pregnancy features of patients with ectopic pregnancy.

	n (%)
Previous surgery history	
+	29 (35.8)
-	52 (91.4)
Previous ectopic pregnancy	
+	8 (9.9)
-	73 (90.1)
Intraabdominal free fluid	
+	11 (13.6)
-	70 (86.4)
Chronic Disease	
+	7 (8.6)
-	74 (91.4)

Table 3. Mass size, β -hCG levels and single dose MTX success rate of patients.

β-hCG (mIU/ml) [median (min-max)]	1763 (129-67854)
Mass size (mm) [mean (\pmSD)]	9.3 (\pm 6.1)
Single dose MTX success [n (%)]	
+	42 (51.9)
-	39 (48.1)

β -hCG: beta-human chorionic gonadotropin, min: minimum, max: maximum, ml: mililiter, mm: milimeter, MTX methotrexate, SD: standart deviation

Table 4. The comparison of age, pregnancy week, mass size, β -hCG levels and intraabdominal free fluid with single dose MTX success.

	Single dose MTX success		<i>p</i>
	+	-	
Age (year) [mean (\pmSD)]	29.8 (\pm 5.3)	31.1 (\pm 4.9)	0.275
Gestational week (year) [median (min-max)]	5 ⁺³ (2 ⁺³ -17 ⁺⁴)	6 (3-14)	0.140
β-hCG (mIU/ml) [median (min-max)]	2101 (48-67854)	1509 (1-7370)	0.152
Mass size (mm) [mean (\pmSD)]	5 (2-10)	4 (0-35)	0.881

β -hCG: beta-human chorionic gonadotropin, min: minimum, max: maximum, ml: mililiter, mm: milimeter, MTX methotrexate, SD: standart deviation