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# Recurrent ectopic pregnancy risk factors and clinical features: a case-control study in Turkey

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## ABSTRACT

**Objectives:** The aim of this study was to identify potential risk factors for recurrent ectopic pregnancy (REP) by comparing patients who developed REP with those who developed intrauterine pregnancy (IUP) after ectopic pregnancy (EP) and non-pregnant (NonP) patients after EP.

**Material and methods:** This study is a single-center retrospective case-control study conducted between January 2016 and January 2020. There were 138 patients in the REP group, 251 patients in the IUP group and 101 patients in the NonP group. Multivariate logistic regression analysis was used to determine risk factors for REP.

**Results:** Presence of a miscarriage history (REP-IUP OR: 14.47 [5.97-35.09]; REP-NonP OR: 12.78 [5.40-30.28]), treated with ART (REP-IUP OR: 55.28 [18.80-162.56]; REP-NonP OR: 5.51 [3.06-9.90]), history of PID (REP-IUP OR: 2.69 [1.83-3.95], REP-NonP OR: 4.80 [3.16-7.32]), previous pelvic surgery (REP-IUP OR: 3.03 [1.69- 5.43]; REP-NonP OR: 1.55 [0.91-2.65]), a history of ruptured ectopic pregnancy at the time of diagnosis (REP-IUP: 7.92 [4.91-12.7], REP-NonP: 14.72 [8.55-25.37]) and salpingotomy, milking surgery and methotrexate treatment increased REP.

**Limitations:** First, the study is a retrospective study. In the interviews, some data may have been remembered incorrectly and accordingly there may be bias. Secondly, the relationship between contraceptive methods and REP could not be evaluated clearly since there were no patients using non-IUD and COC contraceptive methods.

**Conclusions:** Gynecological and obstetric histories of patients with EP, treatment methods of previous EP and complications developing in previous EP change the risk of REP. Therefore, diagnosis and treatment management of EP patients is crucial.

**KEY WORDS:** recurrent ectopic pregnancy, risk factors, salpingotomy, ART therapy, ınflammatory pelvic disease.

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## INTRODUCTION

Ectopic pregnancy (EP) is one of the most common gynecological emergencies [1]. Although mortality decreases with early diagnosis and treatment, ruptured EP is still one of the causes of maternal death in the first trimester [2].

One of the late complications of ectopic pregnancy is recurrent ectopic pregnancy (REP). The risk of REP for women with a previous history of EP has increased by about five to ten times in the general population without an EP history, and was reported at 10-27% [3]. Risk factors defined for EP are past tubal surgery, pelvic inflammatory disease (PID) history, smoking, and treatment with assisted reproductive techniques (ART) [4]. However, the extent to which these factors affect REP development has not yet been fully explained. Moreover, cur-

rent studies are investigating the relationship between the clinical findings and treatment of the previous EP and the risk of REP.

The aim of this study was to identify potential risk factors for REP by comparing patients who developed REP with those who developed intrauterine pregnancy (IUP) after EP and non-pregnant (NonP) patients after EP.

## MATERIAL AND METHODS

### STUDY POPULATION

This study is a single-center retrospective case-control study conducted between January 2016 and January 2020. It has been approved by the local ethics committee, ensuring that the privacy of all participants' data is protected and written consent has been obtained from them and/or their legal representatives.

Between these dates, 736 patients who were diagnosed with ectopic pregnancy among 139 973 patients admitted to the hospital outpatient clinics and emergency room were identified. Of these patients, 549 patients who were followed up with ectopic pregnancy treatment were evaluated. Exclusion criteria were the age of 18 and under, age 45 and over, history of cardiovascular disease and venous thromboembolic disease, history of chronic disease such as diabetes mellitus, epilepsy, any history of malignancy and/or secondary chemotherapy-radiotherapy treatment.

### COLLECTION AND ANALYSIS OF PATIENT DATA

Anamnesis, gynecological examination and imaging results, and treatment of the 521 patients who remained after exclusion criteria from 549 patients diagnosed with ectopic pregnancy were examined retrospectively from the hospital database. 31 patients whose data and/or contact information were not available were excluded from the study. As a result, four hundred ninety patients were included in the study.

Of these 490 patients, the patient group who developed REP after ectopic pregnancy was determined as the case group. As the control group, the patient group with natural IUP after ectopic pregnancy and the NonP after ectopic pregnancy were determined.

The patients were contacted and questioned face to face about treatment history with obstetric history (parity, abortion), body mass index (BMI), invitro fertilization (IVF) or other ART, history of PID, surgical history (previous cesarean section [C/S], diagnostic hysteroscopy, ovarian cystectomy and myomectomy), and contraceptive methods used by the patient (non-medical contraceptive methods, copper intrauterine device [IUD], oral contraceptive pill use [COC]). In the previous ectopic pregnancy, the age of the gestational sac (GS), the location and size of the ectopic pregnancy, whether the previous ectopic gestational sac was ruptured/unruptured, and the ectopic pregnancy treatment method (therapeutic curettage, methotrexate application, salpingectomy, salpingotomy, milking and salpingooforectomy) were determined from the database, confirmed and noted.

### STATISTICAL ANALYSIS

Statistical analyses were performed using SPSS 22 (International Business Machines Corp., Armonk, New York). All values were calculated using mutual tests. The Pearson $\chi^2$ test was used to calculate the differences in previous surgery, PID history, abortion history, ectopic pregnancy location and rupture status at the time of diagnosis, assisted reproductive techniques after ectopic pregnancy, and recurrent ectopic pregnancy rate.

Using univariate conditional logistic regression analysis, we calculated the raw probability rates (OR) and 95% confidence intervals (CI) for each variable. A multivariate logistic regression analysis was used to adjust potential discrepancies and calculate the adjusted odds ratio (AOR). $P < 0.05$ was considered statistically significant.

## RESULTS

There were 490 patients and three groups in this study. 138 were in the REP group, 251 were in the IUP group, and 101 were in the NonP group. The average age of 490 patients included in the study was 27.86 ± 3.73 (min 20 – max 35).

### PATIENT HISTORY AND DEMOGRAPHIC FEATURES

Patients' age, obstetric histories (history of abortus and parity), the contraceptive method they used (non-medical, IUD and COC) and BMI (< 25, 25-29.99, ≥ 30) are given in Table 1.

The patients were divided into two groups as under thirty and thirty and over. When the REP and IUP (REP-IUP OR: 0.43 [0.31-0.60]) were compared in the age group of under thirty years old, REP risk was decreased. In the group of thirty years old and above, when REP and IUP were compared (REP-IUP OR: 0.274 [0.17-0.42]) REP risk was decreased. When REP and NonP were compared (REP-NonP OR: 29.08 [8.90-94.96]) REP risk was significantly increased. When the relationship between the groups' BMI and REP was examined, compared to REP and IUP, REP risk (REP-IUP OR: 0.14 [0.09-0.21]) was decreased in normal BMI (BMI < 25) ($p < 0.001$). In obese patients (BMI ≥ 30), when REP and NonP were compared (REP-NonP: 2.80 [1.46-5.38]), REP risk was increased ($p = 0.002$) (Table 1).

When the obstetric histories were examined, in the presence of an abortion history in groups (REP-IUP OR: 14.47 [5.97-35.09]; REP-NonP OR: 12.78 [5.40-30.28]) REP risk increased. In those with a history of multiparity, REP increased compared with NonP (REP NonP OR: 2.24 [1.54-3.25]) ($p <0.001$) (Table 1).

The frequency of REP (REP-IUP OR: 0.021 [0.006-0.080], REP-NonP OR: 0.256 [0.066-0.994]) decreased in IUD users ($p <0.001$, $p = 0.049$). There was no relationship between COC use and REP frequency ($p = 0.054$).

**TABLE 1.** Patient clinical and demographic features multivariate analysis

| Factor | REP | IUP | NonP | $OR_1$ (95 % CI) | $OR_2$ (95 % CI) | $p_1$ | $p_2$ |
|---|---|---|---|---|---|---|---|
| Age | | | | | | | |
| < 30 | 79 | 137 | 98 | 0.43 (0.31-0.60) | 0.74 (0.52-1.05) | < 0.001 | 0.092 |
| ≥ 30 | 59 | 114 | 3 | 0.27 (0.17-0.42) | 29.08 (8.90-94.96) | < 0.001 | < 0.001 |
| BMI | | | | | | | |
| < 25 | 52 | 164 | 45 | 0.147 (0.09-0.21) | 1.19 (0.76-1.85) | < 0.001 | 0.431 |
| 25-29.99 | 48 | 44 | 38 | 1.11 (0.67-1.86) | 1.41 (0.84-2.38) | 0.66 | 0.18 |
| ≥ 30 | 38 | 43 | 18 | 0.81 (0.46-1.43) | 2.80 (1.46-5.38) | 0.47 | 0.002 |
| Obstetric history | | | | | | | |
| Abortus | 45 | 9 | 10 | 14.47 (5.97-35.09) | 12.78 (5.40-30.28) | < 0.001 | < 0.001 |
| Parity | | | | | | | |
| 0-2 | 34 | 103 | 54 | 0.18 (0.11-0.29 | 0.54 (0.33-0.89) | < 0.001 | 0.016 |
| ≥ 2 | 104 | 148 | 57 | 0.55 (0.39-0.76) | 2.24 (1.54-3.25) | < 0.001 | < 0.001 |
| Contraceptive method | | | | | | | |
| Non-medical method used | 118 | 204 | 80 | 0.40 (0.30-0.53) | 1.72 (1.24-2.38) | < 0.001 | 0.001 |
| IUD | 3 | 38 | 10 | 0.02 (0.00-0.08) | 0.25 (0.06-0.99) | < 0.001 | 0.049 |
| COC | 17 | 9 | 11 | 2.64 (0.98-7.12) | 2.00 (0.77-5.22) | 0.054) | 0.153 |

*REP – recurrent ectopic pregnancy case group, IUP – intrauterine pregnancy group, NonP – nonpregnant group, BMI – body mass index, IUD – intrauterine device, COC – combined oral contraceptives, $OR_1$ – odds ratio for REP-IUP, $OR_2$ – odds ratio for REP-NonP, CI – confidence interval*

Previous surgical history (C/S, diagnostic hysteroscopy, myomectomy, cystectomy), history of ART treatment, history of PID are given in Table 2.

In addition, those with a history of IVF treatment had increased REP frequency (REP-IUP OR: 14.50 [6.9-30.28], REP-NonP OR: 21.77 [3.73-127.02]). Similarly, the frequency of REP (REP-IUP OR: 55.28 [18.80-162.56], REP-NonP OR: 5.51 [3.06-9.90]) increased in those treated with other ART ($p < 0.001$).

In those with a history of PID, REP risk (REP-IUP OR: 2.69 [1.83-3.95], REP-NonP OR: 4.80 [3.16-7.32]) increased.

Regarding gynecological and surgical histories, REP frequency (REP-IUP OR: 3.03 [1.69-5.43], REP-NonP OR: 1.55 [0.91-2.65]) was increased in patients with previous pelvic surgery (Table 2).

However, in patients with a cesarean section (C/S) history in subgroups, when REP and IUP were compared, REP frequency (REP-IUP OR: 0.18 [0.06-0.55]) decreased. When REP and NonP were compared (REP-NonP OR: 2.695 [1.48- 48.85]) REP frequency increased. In patients with a history of diagnostic hysteroscopy, the frequency of REP frequency increased when REP and NonP were compared (REP-NonP OR: 9.5 (2.73-32.9)) ($p < 0.001$) (Table 2).

**TABLE 2.** Multivariate analysis of data related to pelvic surgery histories of patients

| Data | REP | IUP | NonP | $OR_1$ (95% CI) | $OR_2$ (95% CI) | $p_1$ | $p_2$ |
|---|---|---|---|---|---|---|---|
| History of PID | 121 | 67 | 43 | 2.69 (1.83-3.95) | 4.80 (3.16-7.32) | < 0.001 | < 0.001 |
| History of pelvic surgery | 51 | 24 | 39 | 3.03 (1.69-5.43) | 1.55 (0.91-2.68) | < 0.001 | 0.105 |
| History of C/S | 9 | 21 | 0 | 0.18(0.06-0.55) | 26.95 (1.48-48.85) | 0.003 | 0.026 |
| History of diagnostic histeroscopy | 19 | 11 | 4 | 2.64 (0.98-7.10) | 9.50 (2.73-32.9) | 0.053 | < 0.001 |
| History of other surgery (cystectomy-myomectomy) | 23 | 21 | 6 | 1.17 (0.53-2.59) | 6.24 (2.25-17.29) | 0.687 | < 0.001 |
| History of ART treatment | 51 | 247 | 68 | 0.07(0.05-0.11) | 0.71(0.47-1.05) | < 0.001 | 0.09 |
| IVF | 14 | 0 | 3 | 14.5(6.9-30.43) | 21.77(3.73-127.02) | 0.001 | < 0.001 |
| Other ART | 73 | 4 | 30 | 55.28(18.80-162.56) | 5.51(3.06-9.90) | < 0.001 | < 0.001 |

*REP – recurrent ectopic pregnancy case group, IUP – intrauterine pregnancy group, NonP – nonpregnant group, BMI – body mass index, PID – pelvic inflammatory disease, C/S – cesarean, ART – assisted reproductive techniques, IVF – in vitro fertilization, $OR_1$ – odds ratio for REP-IUP, $OR_2$ – odds ratio for REP-NonP, CI – confidence interval*

**TABLE 3.** Multivariate analysis related to previous ectopic pregnancy clinical features

| Factor | REP | IUP | NonP | $OR_1$ (95% CI) | $OR_2$ (95% CI) | $p_1$ | $p_2$ |
|---|---|---|---|---|---|---|---|
| Previous EP site | | | | | | | |
| Tubal ampullar | 109 | 226 | 76 | 0.29 (0.22-0.39) | 1.59 (1.14-2.21) | < 0.001 | 0.006 |
| Tubal isthmic | 7 | 2 | 3 | 7 (1.04-46.95) | 4.2 (0.73-23.90) | 0.045 | 0.106 |
| Tubal fimbrial | 12 | 10 | 5 | 1.36 (0.49-4.04) | 3.52 (1.02-12.07) | 0.58 | 0.045 |
| Tubal cornual | 10 | 6 | 7 | 2.17 (0.62-7.55) | 1.75 (0.52-5.90) | 0.21 | 0.361 |
| Cervix | 0 | 1 | 4 | 0.27 (0.00-8.46) | 0.03 (0.00-0.94) | 0.458 | 0.046 |
| Scar | 0 | 2 | 4 | 0.13 (0.00-3.62) | 0.04 (0.00-1.12) | 0.235 | 0.058 |
| Ovary | 0 | 4 | 2 | 0.04 (0.00-1.12) | 0.13 (0.00-3.62) | 0.058 | 0.235 |
| Previous GS size | | | | | | | |
| < 3 cm | 71 | 245 | 32 | 0.07 (0.04-0.10) | 2.33 (1.49-3.64) | < 0.001 | < 0.001 |
| 3-6 cm | 38 | 3 | 61 | 19.59 (5.80-66.15) | 0.39 (0.22-0.70) | < 0.001 | 0.001 |
| ≥ 6 cm | 29 | 3 | 8 | 32.51 (8.29-127.45) | 10.54 (3.72-29.84) | < 0.001 | < 0.001 |
| Status of ectopic sac | | | | | | | |
| Rupture | 121 | 37 | 22 | 7.92 (4.91-12.7) | 14.72 (8.55-25.37) | < 0.001 | < 0.001 |
| Unrupture | 17 | 214 | 79 | 0.02 (0.01-0.04) | 0.17 (0.09-0.29) | < 0.001 | < 0.001 |

*EP – ectopic pregnancy, REP – recurrent ectopic pregnancy case group, IUP – intrauterine pregnancy group, NonP – nonpregnant group, GS – gestataional sac, cm – centimeters, $OR_1$ – odds ratio for REP-IUP; $OR_2$: odds ratio for REP-NonP; CI: confidence interval*

## MULTIVARIATE ANALYSIS RELATED TO PREVIOUS ECTOPIC PREGNANCY CLINICAL FEATURES AND TREATMENT METHODS

Tables 3 and 4 show the location and size of ectopic pregnancy, whether it was ruptured at the time of diagnosis, gestational sac measurements at the time of diagnosis, and treatments for ectopic pregnancy.

The frequency of REP (REP-IUP: 7.92 [4.91-12.7], REP-NonP: 14.72 [8.55-25.37]) increased in those who had a history of ruptured ectopic pregnancy at the time of diagnosis.

Compared with REP IUP (REP-IUP OR: 19.59 [5.80-66.15]) in patients with an average sac size of 3-6 cm at the time of diagnosis, REP frequency increased compared to the NonP group (REP-NonP OR: 0.39 [0.22- 0.70]) REP frequency was decreased ($p = 0.001$) (Table 2).

In those with an average sac size larger than 6 cm, REP frequency (REP-IUP OR: 32.51 [8.29-127.45], REP-NonP OR: 10.54 [3.72-29.84]) increased ($p <0.001$).

Regarding ectopic pregnancy treatment methods, REP frequency was increased in patients with salpingotomy and milking surgery history and in patients treated with methotrexate ($p < 0.001$) (Table 4).

Regarding ectopic pregnancy treatment methods, REP frequency was increased in patients with salpingotomy and milking surgery history and in patients treated with methotrexate. In contrast, only in patients undergoing therapeutic curettage and in the group of patients undergoing salpingectomy, REP was found to be reduced when REP and IUP were compared ($p < 0.001$) (Table 4).

When ectopic gestational sac locations are compared, tubal ampoules located in the region of ectopic pregnancies are decreased when REP frequency is compared to IUP (REP-IUP OR: 0.29 [0.22-0.39]) is decreased, while REP and NonP are compared (REP-NonP OR: 1.59 [1.14-2.21]) REP frequency increased (Table 3). There was no statistically significant difference between the groups for other comparisons.

**TABLE 4.** Multivariate analysis related to previous ectopic pregnancy treatment

| Treatment of last EP | REP | IUP | NonP | $OR_1$ (95% CI) | $OR_2$ (95% CI) | $p_1$ | $p_2$ |
|---|---|---|---|---|---|---|---|
| Therapeutic curettage | 2 | 116 | 11 | 0.002 (0.00-0.008) | 0.16 (0.03-0.77) | $p < 0.001$ | $p = 0.022$ |
| Salpengectomy | 28 | 92 | 29 | 0.14 (0.085-0.243) | 1.38(0.74-2.59) | $p < 0.001$ | $p = 0.305$ |
| Salpingotomy | 49 | 13 | 12 | 9.49 (4.41-20.45) | 10.12(4.62-22.17) | $p < 0.001$ | $p < 0.001$ |
| Methotrexate treatment | 39 | 14 | 40 | 4.07 (2.02-8.22) | 0.95(0.53-1.71) | $p < 0.001$ | $p = 0.882$ |
| Milking | 20 | 5 | 7 | 9.00 (2.73-29.66) | 5.95 (1.97-17.92) | $p < 0.001$ | $p = 0.002$ |
| Salpingooopherectomia | 0 | 11 | 2 | 0.008 (0.00-0.18) | 0.17 (0.007-3.92) | $p = 0.003$ | $p = 0.269$ |

*EP – ectopic pregnancy, REP – recurrent ectopic pregnancy case group, IUP – intrauterine pregnancy group, NonP – nonpregnant group, $OR_1$ – odds ratio for REP-IUP, $OR_2$ – odds ratio for REP-NonP, CI – confidence interval*

## DISCUSSION

Having a history of miscarriage, a history of PID, treatment with ART, a gynecological surgery history, ectopic GS greater than 6 cm at the time of diagnosis, previous EP GS rupture, methotrexate treatment use in previous EP therapy, salpingotomy and milking are risk factors for REP (Table 5).

Being under the age of thirty, having a history of IUD use, having a normal BMI, and having a salpingectomy in previous EP treatment reduce the risk of REP.

Many studies have reported that infertility history and history of treatment with ART increase the risk of EP and REP [5-9]. It may be caused by the embryo being placed in the tubal cavity instead of the intrauterine cavity in those undergoing ART treatment, and may be a risk factor for REP by causing tubal damage during the procedure. Although there is a study indicating otherwise [10], ART treatment is stated as an important risk factor for REP in this study.

In some studies, it has been shown that spontaneous miscarriage history and increase in the number of abortus increase the risk of REP [8, 10]. On the other hand, there are studies indicating that there is no relationship between the history of miscarriage and the risk of REP [5, 9]. Levin *et al.* [11] stated that the changes caused by the miscarriage in the endometrium and microenvironment increase the risk of REP. The fact that miscarriage increases the risk of REP in this study supports these findings.

In a study by Cheng Li *et al*., the history of PID was identified as a risk factor for EP, and there are many studies indicating that PID is a risk factor for ectopic pregnancy [12-14]. In contrast to these studies, in a case-control study conducted with 91 REP patients, no relation was found between the history of PID and REP [15]. The inflammatory response and salpingitis developing in PID cause tubal structural abnormalities and adhesions. Accordingly, tubal epithelium cilia activity and tubal smooth muscle activity are impaired. Therefore, tubal implantation may develop [12, 13]. According to the results of this study, PID is an important factor that increases the risk of REP. It supports these publications. Moreover, the number of REP and OR values in our study makes these data strong.

In previous studies, the relationship between REP risk and GS diameter, presence of hemoperitoneum, βhCG levels and REP risk was investigated [8, 15]. However, no significant relationship was found. In this study, the risk of REP was increased in patients with a previous EP GS size of more than 6 cm, and in patients where GS was ruptured in the previous EP. This finding shows that early diagnosis and prevention of complications can prevent late complications such as REP. However, larger studies may be needed to investigate these data.

Levin *et al.* [10] stated that previous pelvic and uterine surgery was a risk factor for REP in their study. This finding has been corroborated in many other publications [7, 9, 15, 16]. Pelvic surgery may create a risk factor for REP by causing tubal damage and adhesions [17].

There are many studies investigating the relationship between the previous EP treatment method and REP. Li *et al.* found that the risk of REP is increased in patients treated with previous EP medical methods (such as methotrexate treatment) [9]. Levin *et al.* [10] likewise stated that the rate of REP is low in patients with successful medical treatment. It is not surprising that we know that these surgical procedures cause tubal damage [17]. However, it is still a question of which surgical procedures increase the risk of REP more. In two studies evaluating the development of REP in patients who were followed up for 24 months after surgical EP treatment, it was found that the risk of REP was decreased in patients who underwent salpingotomy [18, 19]. In a study investigating the surgical method to be selected in patients who develop EP after infertility treatment, it was found that salpingotomy has a high REP risk and a single dose of methotrexate after treatment may decrease the risk of REP [20]. It was reported in this study that radical approaches such as salpingectomy in EP surgery reduce the risk of REP but also decrease the fertility rate [20]. It was also reported that postoperative adhesions and trophoblastic implantation increase with salpingotomy [20]. Hurrel *et al.* reported that the rate of REP was lower in patients undergoing salpingectomy compared to patients undergoing salpingotomy [15]. However, Wang *et al.* and Zhang *et al.* also reported that salpingotomy is a risk factor for REP [7, 8]. In this study, similar to other studies, salpingotomy increased the risk of REP and salpingectomy reduced the risk of REP. It is reported that the risk of REP is lower in patients undergoing salpingectomy not only when compared to other surgical methods but also when compared with medical methods. In this study, increased REP rates in methotrexate users may also indicate failure in methotrexate treatment.

Li *et al.* reported in their previous studies that they increased the risk of EP when they evaluated the use and duration of IUD together [4, 9], but reported that it reduced the risk of REP only in a study in which IUD use was questioned [17]. As stated in the ACOG guideline, the use of IUD is an effective contraceptive method that prevents pregnancy. Therefore, it can be predicted to reduce the risk of REP. However, the EP rate may increase in pregnancies developing during IUD use [21]. According to this study, the use of IUD reduces the risk of REP. This result may be associated with effective IUD use.

In a previous study, it was stated that advanced maternal age increases the risk of EP [22]. Being under the age of thirty years reduced the risk of REP in this study. As far as the author knows, there is no previous study evaluating the relationship between BMI and REP risk. According to this study, normal BMI reduces the risk of REP. Further comprehensive studies are needed to demonstrate that it reduces the risk of REP.

The study has some limitations. First, the study is retrospective. In the interviews, some data may have been remembered incorrectly and accordingly there may be bias. Secondly, the relationship between contraceptive methods and REP could not be evaluated clearly since there were no patients using non-IUD and COC contraceptive methods. Also, since IUD and COC usage times are not specified, data may be misleading. It would be appropriate to consider these factors before generalizing the data to the society.

As a result, this study clearly shows that miscarriage history, PID history, history of treatment with ART, previous gynecological surgery and salpingotomy surgery in the previous EP are risk factors for REP. Also, late diagnosis of previous EP and developing complications may be risk factors for REP. Effective use of IUD, normal BMI and being under the age of 30 may prevent REP development.

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## DISCLOSURE

The authors report no conflict of interest.

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### AUTHORS' CONTRIBUTIONS

SK prepared research concept and design of the publication. SK, PK, CT collected data. SK, EK, MB analysed data and wrote the article. SK critically revised it.