Anadolu Kliniği
Tıp Bilimleri Dergisi
ISSN: 2149-5254 e-ISSN: 2458-8849
Anadolu Klin/Anatol Clin 2026;31(2):266-273
Original Research / Orijinal Araştırma
https://doi.org/10.21673/anadoluklin.1752432

The impact of treatment modalities for ectopic pregnancy on future fertility outcomes

Ektopik gebelik tedavi yöntemlerinin gelecek fertilite sonuçları üzerine etkisi

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ABSTRACT

Aim: This study aimed to evaluate fertility outcomes in patients managed with medical treatment, surgical treatment, or expectant management for ectopic pregnancy.

Methods: Patients aged 18–45 years who were diagnosed with ectopic pregnancy at the Obstetrics and Gynecology outpatient clinics of Ondokuz Mayıs University between January 2015 and December 2020 were retrospectively evaluated. Patients were categorized into three groups based on treatment modality: medical, surgical, or expectant management. Demographic characteristics, risk factors for ectopic pregnancy, baseline β-hCG levels, treatment success, recurrence rates, and subsequent spontaneous intrauterine pregnancy outcomes were collected and statistically analyzed.

Results: A total of 314 patients were included in the study. There was no statistically significant difference among treatment groups regarding age, previous pregnancy history, or ectopic pregnancy risk factors (all $p > 0.05$). Treatment success rates differed significantly among groups, with the highest in the surgical group (98.6%), followed by the expectant management (94.1%) and medical treatment (72.5%) groups ($p < 0.001$). Recurrent ectopic pregnancy rates were comparable among groups without a statistically significant difference ($p=0.28$). Spontaneous intrauterine pregnancy rates during follow-up differed significantly among treatment groups (40.0% in the medical group, 27.6% in the surgical group, and 52.9% in the expectant group; $p = 0.02$). Baseline β-hCG levels were not significantly associated with treatment success in any treatment modality.

Conclusion: Spontaneous intrauterine pregnancy outcomes differed among treatment modalities in patients with ectopic pregnancy, with lower rates observed following surgical management. These findings suggest an association between treatment modality and subsequent fertility outcomes; however, prospective controlled studies are required to establish causal relationships.

Keywords: Ectopic pregnancy; fertility; surgery

ÖZ

Amaç: Bu çalışmanın amacı, ektopik gebelik nedeniyle medikal tedavi, cerrahi tedavi veya ekspektan yönetim uygulanan hastalarda fertilite sonuçlarının değerlendirilmesidir.

Yöntemler: Ocak 2015 ile Aralık 2020 tarihleri arasında Ondokuz Mayıs Üniversitesi Kadın Hastalıkları ve Doğum polikliniklerinde ektopik gebelik tanısı alan 18–45 yaş arası hastalar retrospektif olarak değerlendirildi. Hastalar uygulanan tedavi yöntemine göre medikal tedavi, cerrahi tedavi ve ekspektan yönetim olmak üzere üç gruba ayrıldı. Demografik özellikler, ektopik gebelik risk faktörleri, başlangıç β-hCG düzeyleri, tedavi başarısı, rekürrens oranları ve takip sürecindeki spontan intrauterin gebelik sonuçları kaydedilerek istatistiksel olarak analiz edildi.

Bulgular: Çalışmaya toplam 314 hasta dahil edildi. Gruplar arasında yaş, önceki gebelik öyküsü ve ektopik gebelik risk faktörleri açısından istatistiksel olarak anlamlı fark saptanmadı ($p > 0.05$). Tedavi başarı oranları gruplar arasında anlamlı farklılık gösterdi ve en yüksek başarı cerrahi grupta (%98.6), ardından ekspektan yönetim (%94.1) ve medikal tedavi (%72.5) gruplarında izlendi ($p < 0.001$). Rekürren ektopik gebelik oranları açısından gruplar arasında anlamlı fark bulunmadı ($p=0.28$). Takip sürecinde spontan intrauterin gebelik oranları gruplar arasında anlamlı farklılık gösterdi (%40.0 medikal, %27.6 cerrahi ve %52.9 ekspektan; $p = 0.02$). Başlangıç β-hCG düzeyleri ile tedavi başarısı arasında herhangi bir tedavi grubunda anlamlı ilişki saptanmadı.

Sonuç: Ektopik gebelik hastalarında uygulanan tedavi yöntemlerine göre spontan intrauterin gebelik sonuçlarının farklılık gösterdiği izlenmiştir. Cerrahi tedavi sonrası spontan intrauterin gebelik oranlarının daha düşük olduğu gözlenmekle birlikte, bu ilişkinin nedenselliğini ortaya koymak için prospektif kontrollü çalışmalara ihtiyaç vardır.

Anahtar Sözcükler: Cerrahi; ektopik gebelik; fertilite

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Received/Geliş : 28.07.2025
Accepted/Kabul: 23.03.2026
Publication Date/Yayımlanma Tarihi: 23.05.2026

Acknowledgements: None
Author Contributions: Conceptualization: GE and FDBG; Design: GE, FDBG and SMA; Supervision: SMA; Materials: GE; Data Collection and/or Processing: GE and SMA ; Analysis and/or Interpretation: GE, FDBG and SMA; Literature Search: GE, FDBG and SMA; Writing: GE, FDBG and SMA; Critical Review: FDBG and SMA. All authors have read and approved the published version of the manuscript.
Ethics Committee Approval: This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Clinical Research Ethics Committee of Ondokuz Mayıs University (Decision no: 2022/483, date: 09.11.2022).
Informed Consent statement: Informed consent was obtained from all participants included in the study.
Data Availability Statement: The data supporting the findings of this study are available from the corresponding author upon reasonable request
Financial Disclosure: No financial support was received from any institution or organization for this research.
Conflict of Interest: The authors declare that they have no conflict of interest to disclose
Artificial Intelligence Statement: The authors used Grammarly and Chat GPT to enhance the language and readability of the manuscript. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the integrity of the published manuscript.

Cite as: Evci G, Bildircin Gokyar FD, Aydin SM. The impact of treatment modalities for ectopic pregnancy on future fertility outcomes. Anatol Clin. 2026;31(2):266-273.

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INTRODUCTION

Ectopic pregnancy is defined as the implantation of a fertilized ovum outside the uterine cavity and accounts for approximately 1–2% of all pregnancies (1,2). It remains a leading cause of maternal mortality in the first trimester (3). The etiology is multifactorial, and recognized risk factors include tubal pathology, endometriosis, previous tubal surgery, intrauterine device use, and assisted reproductive techniques (3,4).

With the widespread use of serial β-hCG measurements and transvaginal ultrasonography, ectopic pregnancies are increasingly diagnosed at earlier stages, allowing for conservative treatment options such as expectant management and medical treatment (5,6). Current management strategies aim not only to resolve the acute condition but also to preserve future fertility, particularly in women of reproductive age (7).

Expectant management, medical treatment with methotrexate, and surgical intervention constitute the primary treatment modalities for ectopic pregnancy (8–10). While conservative approaches have been associated with favorable reproductive outcomes in selected patients, surgical treatment may negatively affect fertility (11–13). However, data comparing fertility outcomes among different treatment modalities remain inconsistent.

Therefore, this study aimed to evaluate fertility outcomes following expectant, medical, and surgical management of ectopic pregnancy and to assess the impact of treatment modality on long-term reproductive potential.

MATERIAL AND METHODS

The retrospective study was conducted with the approval of the Ethics Committee of Ondokuz Mayıs University Faculty of Medicine (Decision no: 2022/483, date: 09.11.2022). Medical records of 1,218 patients diagnosed with ectopic pregnancy between January 2015 and December 2020 were reviewed. From this cohort, 314 patients who met the predefined eligibility criteria were included in the final analysis.

Demographic and clinical characteristics, including age, smoking habits, history of pelvic inflammatory disease, contraceptive methods, previous curettage or abdominal surgeries, use of intrauterine devices, ultrasonographic findings, and treatment outcomes, were recorded for analysis.

Patients were eligible for inclusion if they had a confirmed diagnosis of ectopic pregnancy, completed their treatment at our institution, and had at least 24 months of follow-up data available. Exclusion criteria encompassed missing medical records, failure to contact the patient during follow-up, and concurrent intrauterine pregnancies.

Based on the type of treatment received, patients were categorized into three groups: expectant management, medical treatment, and surgical treatment. Data were collected retrospectively from hospital records, and follow-up information on fertility outcomes was obtained by telephone after verbal informed consent. Treatment approaches were determined based on the patient's clinical condition, hemodynamic stability, serum β-hCG levels, and transvaginal ultrasonography findings. Expectant management was preferred for hemodynamically stable patients without signs of rupture and with declining serial β-hCG levels. Medical treatment was administered to hemodynamically stable patients with unruptured ectopic pregnancy, absence of fetal cardiac activity, and no contraindications to methotrexate therapy. Surgical treatment was chosen in cases of hemodynamic instability, suspected or confirmed rupture, high β-hCG levels, presence of fetal cardiac activity, or contraindications to medical treatment.

The primary outcome of the study was the occurrence of spontaneous intrauterine pregnancy within two years after treatment. Secondary outcomes included the recurrence of ectopic pregnancy, treatment success, and any complications related to the intervention.

Treatment success was defined separately for each management strategy. For the medical treatment group, treatment failure was defined as the need for subsequent surgical intervention due to inadequate decline or plateau of serum β-hCG levels, clinical deterioration, or rupture. For the expectant management group, treatment failure was defined as the requirement for medical (methotrexate) or surgical treatment during follow-up. For the surgical treatment group, treatment failure was defined as the need for additional methotrexate therapy due to insufficient postoperative decline in serum β-hCG levels or the requirement for repeat surgery. Accordingly, treatment success was defined as resolution of ectopic pregnancy without the need for additional medical or surgical intervention.

Statistical Analysis

Data were analyzed using the SPSS Statistics for Windows (Statistical Package for the Social Sciences package program version 21.0, IBM Corp., Armonk, N.Y., USA).. Descriptive statistics were presented as mean ± standard deviation. Data distribution was assessed for normality using the Shapiro–Wilk test. Comparisons among the three treatment groups were performed using one-way ANOVA or the Kruskal–Wallis test, followed by appropriate post-hoc analyses when necessary. Categorical variables were compared using Fisher's exact test. A p-value < 0.05 was considered statistically significant. A post-hoc power analysis was performed based on the primary outcome (spontaneous intrauterine pregnancy rate). Considering the observed effect size (Cramer's V ≈ 0.18) and a total sample size of 314 patients at an alpha level of 0.05, the study demonstrated approximately 80% statistical power. However, subgroup comparisons involving the expectant management group had lower statistical power due to the limited sample size.

RESULTS

A total of 314 patients diagnosed with ectopic pregnancy were included in the study and categorized according to treatment modality as medical treatment (n=80), surgical treatment (n=217), and expectant management (n=17).

Baseline demographic and obstetric characteristics

The mean age of the patients was similar among the treatment groups (28.5 ± 4.8 years in the medical group, 28.6 ± 5.0 years in the surgical group, and 27.3 ± 5.6 years in the expectant group; p = 0.596). Previous pregnancy history did not differ significantly between the groups (p = 0.059). The proportion of patients with at least one previous pregnancy was 73.8% in the medical group, 59.9% in the surgical group, and 52.9% in the expectant group. However, a history of miscarriage was significantly more frequent in the medical treatment group compared with the other groups (48.7%, 21.2%, and 23.5%, p < 0.001) (Table 1).

Comparison of ectopic pregnancy risk factors

No statistically significant differences were observed among treatment groups regarding smoking status (p = 0.95), history of pelvic infection (p = 0.33), curettage history (p = 0.14), oral contraceptive use (p = 0.95), intrauterine device use (p = 0.69), or history of abdominal surgery (p = 0.46) (Table 2).

Clinical findings and treatment outcomes

Detection of an ectopic focus on transvaginal ultrasonography differed significantly among the groups, with the highest frequency in the surgical treatment group (71.0%) compared with the medical (32.5%) and expectant groups (5.9%) (p < 0.001). Treatment success rates were also significantly different between groups, being highest in the surgical group (98.6%), followed by the expectant (94.1%) and medical treatment groups (72.5%) (p < 0.001). Recurrent ectopic pregnancy rates were comparable among the groups, and no statistically significant difference was observed (p=0.28). A significant difference was detected among treatment groups regarding spontaneous intrauterine pregnancy rates during follow-up (40.0% in the medical group, 27.6% in the surgical group, and 52.9% in the expectant group; p = 0.02) (Table 3).

Baseline β-hCG levels according to treatment success

Baseline β-hCG levels were higher in patients with treatment failure than in successfully treated patients across all treatment modalities; however, these differences were not statistically significant in the surgical (p = 0.73), expectant (p = 0.82), or medical treatment groups (p = 0.18) (Table 4).

DISCUSSION AND CONCLUSION

Ectopic pregnancy occurs in approximately 2% of all pregnancies worldwide and mostly affects women of reproductive age. In recent years, the main aim of treatment has been to preserve fertility while minimizing damage to the fallopian tubes (14). In this study, we evaluated the pregnancy rates and the effects of different treatment methods on fertility in patients treated for ectopic pregnancy in our clinic.

The groups showed similar characteristics in terms of age and previous pregnancy history. A history of curettage was most frequently observed in the medical treatment group, and this difference was statistically significant. No significant difference was observed between the groups in terms of other ectopic pregnancy risk factors. Detection of the ectopic pregnancy focus was most frequently observed in the surgical group, and the more frequent preference

Table 1. Baseline demographic and obstetric characteristics

Variable	Medical (n=80)	Surgical (n=217)	Expectant (n=17)	p value
Age (years) mean ± SD	28.5 ± 4.8	28.6 ± 5.0	27.3 ± 5.6	0.596
Previous pregnancy history, n (%)				0.059
No previous pregnancy	21 (26.2)	87 (40.1)	8 (47.1)	
≥1 previous pregnancy	59 (73.8)	130 (59.9)	9 (52.9)	
History of miscarriage, n (%)	39 (48.7)	46 (21.2)	4 (23.5)	**<0.001**

Values are presented as mean ± standard deviation (SD) or number (%). Continuous variables were compared using one-way ANOVA, and categorical variables were compared using Fisher's exact test. A p-value < 0.05 was considered statistically significant. n: Number, %: Percentage.

Table 2. Comparison of ectopic pregnancy risk factors among groups

Risk factor	Medical (n=80)	Surgical (n=217)	Expectant (n=17)	p value
Smoking, n (%)	16 (20.0)	42 (19.4)	1 (5.9)	0.95
History of pelvic infection, n (%)	9 (11.2)	19 (8.8)	0 (0.0)	0.33
Curettage history, n (%)	20 (25.0)	39 (18.0)	1 (5.9)	0.14
Oral contraceptive use, n (%)	5 (6.2)	9 (4.1)	0 (0.0)	0.95
IUD use, n (%)	5 (6.2)	11 (5.1)	1 (5.9)	0.69
History of abdominal surgery, n (%)	30 (37.5)	69 (31.8)	4 (23.5)	0.46

Categorical variables were compared using the chi-square or Fisher's exact test when appropriate; p < 0.05 was considered statistically significant. IUD: Intrauterine Device, n: Number, %: Percentage.

Table 3. Clinical findings and treatment outcomes

Outcome	Medical (n=80)	Surgical (n=217)	Expectant (n=17)	p value
Ectopic focus detected on TVUSG, n (%)	26 (32.5)	154 (71.0)	1 (5.9)	**<0.001**
Treatment success, n (%)	58 (72.5)	214 (98.6)	16 (94.1)	**<0.001**
Recurrent ectopic pregnancy, n (%)	21 (26.3)	36 (16.6)	2 (11.8)	0.28
Spontaneous intrauterine pregnancy, n (%)	32 (40.0)	60 (27.6)	9 (52.9)	**0.02**

Values are presented as a number (%). Comparisons between treatment groups were performed using the chi-square test. A p-value < 0.05 was considered statistically significant. TVUSG: Transvajinal Ultrasonografi, n: Number, %: Percentage.

Table 4. Baseline β-hCG levels according to treatment success

Treatment group	Successful treatment, mean ± SD (n)	Failed treatment, mean ± SD (n)	p value
Medical	1387.4 ± 1885.7 (n=58)	1994.4 ± 2433.4 (n=22)	0.18
Surgical	5100.5 ± 6351.2 (n=214)	8533.7 ± 13078.9 (n=3)	0.73
Expectant	512.8 ± 421.1 (n=16)	525.0 (n=1)	0.82

Values are presented as mean ± standard deviation (SD) and number of patients (n). The standard deviation could not be calculated for groups containing a single patient. Comparisons were performed using the Mann–Whitney U test. n: Number, %: Percentage.

for surgical treatment in patients with detected foci was considered to be related to this situation. The treatment success rate was highest in the surgical group, whereas the spontaneous pregnancy rate was lowest. The highest spontaneous pregnancy rate was observed in the expectant group. The fact that all patients underwent salpingectomy was considered an important factor that could explain the negative impact on fertility due to decreased tubal reserve. When β-hCG levels of successful and unsuccessful patients were compared based on treatment outcomes, no significant difference was observed between the groups.

In the review by Kirk et al., previous studies on expectant management reported intrauterine pregnancy rates ranging from 63% to 88% and recurrence rates of approximately 4–5%. It was shown that the strongest predictor of treatment success was the initial serum β-hCG level; while the success rate was 88% at values below 200 mIU/mL, it decreased to 25% at levels above 2000 mIU/mL. In addition, in long-term follow-up, the tubal patency rate was reported to be 93%, and the average pregnancy duration was 16 months (15). Similarly, other studies have shown that spontaneous resolution rates can reach up to 90% in patients with baseline β-hCG levels below 1000 IU/mL (16,17).

In our study, no significant difference in baseline β-hCG mean was observed between successful and unsuccessful cases among expectant patients. However, it should be noted that all patients in the expectant group had baseline β-hCG levels below 1000 IU/mL. In this group, treatment success was 94.1%, and the subsequent pregnancy rate was 52.9%. However, the small number of patients in the expectant group may have limited comparability between the groups.

Transvaginal ultrasonography (TVUSG) is an important tool in predicting treatment success in patients undergoing expectant management. Previous studies have shown a reduction in ectopic mass size on day 3 in 55% of cases and on day 7 in 84%. In particular, the reduction in mass observed on day 7 has been reported to have 84% sensitivity and 100% specificity in predicting spontaneous resolution (18). These findings demonstrate that expectant management can be safely applied with close TVUSG monitoring when appropriate patient selection is made. It has been reported that there is no significant difference in spontaneous pregnancy rates between patients who underwent primary surgical treatment and those who developed surgical requirements after unsuccessful expectant management (19). Baggio et al., however, showed that intrauterine pregnancy rates after expectant management were similar to those obtained after methotrexate treatment and were higher compared to surgical treatment. In the study in question, fertility rates were reported as 65% for expectant treatment, 55% for methotrexate treatment, and 39% for surgical treatment; it was emphasized that more favorable reproductive outcomes were obtained after conservative approaches (20). These data, consistent with our findings, show that non-surgical management strategies play an important role in preserving fertility in appropriately selected patients.

In the study by Kumtepe and Kadanalı, the effectiveness of methotrexate treatment was evaluated in hemodynamically stable, ruptured, and non-ruptured ectopic pregnancy cases, and a success rate of 62% was reported in suspected rupture cases. However, in this study, the presence of free peritoneal fluid was accepted as a rupture criterion, and a consistent distinction could not be made between true tubal rupture and tubal abortion. The authors also stated that blood detected in the Douglas pouch does not always indicate tubal rupture and may be associated with tubal abortion (21). This suggests that decreases in β-hCG observed after methotrexate treatment may not always be due solely to the drug's pharmacological effect. Indeed, in some cases, this decrease may reflect spontaneous regression. In our study, expectant management was successful in hemodynamically stable patients with decreased β-hCG levels. Including such cases in the medical treatment group may lead to a higher-than-expected methotrexate success rate. Therefore, changes in β-hCG levels, especially in the presence of free peritoneal fluid, should be interpreted carefully, and the possibility of tubal abortion should be considered in the differential diagnosis. In the literature, generally positive reproductive outcomes are reported after methotrexate treatment in ectopic pregnancy. Tubal patency rates assessed by hysterosalpingography have been reported to range between 77–82%, and pregnancy rates after a single dose of methotrexate can reach up to 80% (22). In another study, the total pregnancy rate was reported as 79%, with 87% of these pregnancies being intrauterine and 12% being recurrent ectopic pregnancies (23). Scarpelli et al. emphasized that methotrexate is a safe and fertility-preserving treatment option when appropriate patient selection is made (24).

In our study, the medical treatment success rate was 72%, the spontaneous intrauterine pregnancy rate was 40%, and the recurrence rate was 26%. Although our pregnancy rate is lower compared to some previous studies, our recurrence rate is within the ranges reported in the literature. These differences can be explained by factors such as patient selection, initial fertility characteristics, and the inclusion of patients with higher initial β-hCG levels or more complex clinical presentations. Similarly, Hao et al. emphasized that reproductive outcomes may be more affected by patient-related factors than by the treatment method (25). Our findings are consistent with the literature showing that methotrexate treatment is associated with positive reproductive outcomes when appropriate patient selection is made. Jamard et al. evaluated the recurrence and fertility outcomes after salpingotomy and salpingectomy; they reported intrauterine pregnancy rates of 88% and 68%, and recurrence rates of 8% and 5%, respectively. However, no statistically significant difference was found between the two surgical techniques regarding fertility or recurrence (26). Similarly, Turan et al. reported spontaneous pregnancy rates of 65.2% after salpingectomy and 60% after salpingostomy, showing no significant difference between the groups (27). However, some long-term studies have suggested that the cumulative intrauterine pregnancy rates over 7 years may be lower in the salpingectomy group (28). Li et al. reported pregnancy rates of 50.9% after salpingostomy and 55.5% after salpingectomy, but again found no statistically significant difference between the two methods (29).

Since all patients in our surgical group underwent salpingectomy, it was not possible to compare different surgical techniques. In our study, the recurrence rate after surgical treatment was 16.6%, which is close to the approximately 10% reported by Alice et al. (30).

In contrast to our study, Bestel et al. emphasized the importance of individualized treatment decisions. They reported that there was no significant difference in fertility outcomes between the expectant, medical, and surgical treatment groups (31). Similarly, in another study comparing surgical and medical treatment, pregnancy rates of 76% after medical treatment, 76% after laparoscopic salpingostomy, and 67% after laparoscopic salpingectomy were reported. Although pregnancy rates appeared to be lower after radical surgery, no statistically significant difference was observed between the groups (32). In our cohort, recurrence rates were 26.3% in the medical group, 11.8% in the expectant group, and 16.6% in the surgical group. Treatment success rates were calculated as 94% for expectant management, 98% for surgical treatment, and 72% for medical treatment. Spontaneous intrauterine pregnancy rates were 52.9% in the expectant group, 40.0% in the medical group, and 27.6% in the surgical group, with a statistically significant difference between the groups. However, no significant differences were observed in pairwise comparisons, particularly given the small sample size in the expectant group.

The findings suggest that fertility outcomes depend not only on the treatment method applied but also on patient characteristics and initial clinical condition. Due to the study's retrospective design and the lack of multivariate analyses, these results reflect a correlation rather than causality. Therefore, prospective studies with sufficient sample sizes are needed to reveal the true effects of different treatment approaches on fertility.

Acknowledgements: The authors would like to thank the clinical secretarial staff for their assistance in accessing and organizing archived patient records, and the statistical unit for their technical support during the analysis process.

Author Contributions: Conceptualization: GE and FDBG; Design: GE, FDBG and SMA; Supervision: SMA; Materials: GE; Data Collection and/or Processing: GE and SMA ; Analysis and/or Interpretation: GE, FDBG and SMA; Literature Search: GE, FDBG and SMA; Writing: GE, FDBG and SMA; Critical Review: FDBG and SMA. All authors have read and approved the published version of the manuscript.

Ethics Committee Approval: This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Clinical Research Ethics Committee of Ondokuz Mayıs University (Decision no: 2022/483, date: 09.11.2022).

Informed Consent statement: Due to the study's retrospective design and the use of archived patient records, the Ethics Committee waived the requirement for informed consent.

Data Availability Statement: The data supporting the findings of this study are available from the corresponding author upon reasonable request

Financial Disclosure: No financial support was received from any institution or organization for this research.

Conflict of Interest: The authors declare that they have no conflict of interest to disclose

Artificial Intelligence Statement: The authors used Chat GPT to enhance the language and readability of the manuscript. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the integrity of the published manuscript.

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