

Subject Area: Obstetrics and Gynecology

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Recommended Citation

Dawood, Ayman S.; Borg, Hesham M.; and Omar, Mona K. (2022) "Anatomical changes and ovarian reserve assessment following methotrexate therapy in tubal ectopic pregnancy," *Journal of Medicine in Scientific Research*: Vol. 5: Iss. 2, Article 14.

DOI: https://doi.org/10.4103/jmisr.jmisr_74_21

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Anatomical changes and ovarian reserve assessment following methotrexate therapy in tubal ectopic pregnancy

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Abstract

Background

Methotrexate (MTX) therapy for ectopic pregnancy (EP) is widely used as an alternative for surgical treatment. Its effects on ovarian reserve or pelvic anatomy are not well established.

Aims

The aim was to evaluate anatomical changes and ovarian reserve in cases of tubal EP treated by MTX therapy.

Materials and methods

A prospective cohort study was conducted at Tanta University. All patients with EP were enrolled. Eligible patients were treated by MTX. Ovarian reserve was assessed by anti-Mullerian hormone (AMH) level and antral follicle count (AFC) 3 months after treatment. Anatomical changes were assessed by laparoscopy 6 months after treatment.

Statistical analysis used

Mean, SD, χ^2 test, and Student's *t*-test were used.

Results

The mean age was 28.24 ± 5.48 years, and the mean BMI was 21.85 ± 4.58 . The basal β -human chorionic gonadotropin was 1788.48 ± 1171.92 mIU/ml. The mean gestational age was 42.6 ± 6.0 days. Serum level of AMH was 3.98 ± 1.11 and 3.54 ± 1.49 before and after MTX therapy, respectively, with no significant difference between AMH levels before and after therapy ($P = 0.243$). AFC after treatment was within normal range, with no significant difference in AFC before and after treatment, ($P = 0.251$). Peritubal and periovarian adhesions were the most common anatomical changes noticed during laparoscopy.

Conclusion

MTX therapy is a safe and effective alternative to surgery for undisturbed tubal EP. Two-dose MTX regimen did not compromise ovarian reserve or affect pelvic anatomy.

Keywords: Ectopic pregnancy, laparoscopy, methotrexate, ovarian reserve, serum AMH

INTRODUCTION

Ectopic pregnancy (EP) is a life-threatening condition if not early diagnosed and properly managed. The Center for Disease Control and Prevention (CDC) reported an estimated prevalence of EP of 2% of all pregnancies. In addition, EP accounts for 9% of maternal mortality causes [1]. Nowadays, EP has a high incidence owing to widespread access to assisted reproductive technologies,

greater prevalence of sexually transmitted diseases, and increased incidence of pelvic inflammatory diseases, especially owing to chlamydia trachomatis infections [2].

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Access this article online

Quick Response Code:



Website:
www.jmsr.eg.net

DOI:
10.4103/jmsr.jmsr_74_21

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Submitted: 24-Oct-2021 Revised: 30-Nov-2021 Accepted: 18-Dec-2021 Published: 09-Aug-2022

How to cite this article: Borg HM, Omar MK, Dawood AS. Anatomical changes and ovarian reserve assessment following methotrexate therapy in tubal ectopic pregnancy. J Med Sci Res 2022;5:171-6.

Accurate diagnosis of EP can be commenced at early stages through the use of transvaginal ultrasound (TVS) and measurement of human chorionic gonadotropin serum (HCG). On the contrary, laparoscopy is used in surgical treatment intervention [3]. There also exists a small group of women with a positive pregnancy test and an uncharacteristic image in TVS testing, described in the literature as pregnancy of unknown location [2].

The introduction of medical treatment with methotrexate (MTX) for EP led to a change in EP from an emergency condition to a more benign one even in symptomatic patients [4]. Moreover, medical treatment could be given on an outpatient basis in hemodynamic patients in close adherence to medical services. Stowall *et al.* [5] introduced medical treatment of EP firstly in 1991. Later on, many studies were conducted on this issue, but the first randomized clinical trial on the success of MTX in EP was conducted in 1997, which compared MTX with laparoscopic salpingotomy [6].

Researchers have conducted many studies to assess the success rate of MTX treatment in EP where the reported rates ranged from 65 to 95%. This wide success range of MTX was owing to difference in inclusion criteria and doses of MTX. A Cochrane meta-analysis was concluded to assess the correlation between HCG titer and success of MTX in EP. They reported that the highest success rate was obtained when HCG levels were not more than 3000 IU/ml [4]. MTX is not fully safe. It has some adverse effects, especially if multiple doses were given. MTX impairs quality of life when compared with laparoscopic surgery. It was reported that 61% receiving MTX experienced complications or adverse effects compared with 12% in laparoscopic surgery [4]. MTX as a single-dose therapy had fewer adverse effects with nearly similar success rate to a multiple-dose regimen [7].

Regarding the pregnancy rate following MT therapy for EP, studies have reported different rates. Hajenius and colleagues followed cases in MT and laparoscopic surgery for 18 months. They reported rates of 36% and 43% for MT and surgery, respectively [6]. Hajenius and colleagues concluded that MTX was not superior to surgery regarding future fertility. They linked this finding to the use of multiple-dose regimen (three doses), which might have induced local endometrial damage, leading to lower pregnancy rates. On the contrary, other studies used MT in a dose of 1 mg/kg and reported pregnancy rates up to 67% compared with 56–89% after surgery [6].

Future fertility is an important issue to be considered when medical treatment of EP is chosen [6]. The effects of MT on ovarian reserve are not well known. The ovarian reserve could be assessed by anti-Mullerian hormone (AMH), which is considered a keystone marker, being independent of the menstrual cycle and has higher reproducibility than other markers [8]. The tubal patency in women treated by MTX can be determined by hysterosalpingography [9].

MATERIALS AND METHODS

Study design and settings

This interventional prospective cohort study was conducted at the Department of Obstetrics and Gynaecology, Tanta University, through March 1, 2015, to September 30, 2016.

Sample size justification

The least sample size needed, calculated using Epi info version 7 (CDC, Atlanta, Georgia, USA), was 30 (two-sided confidence level 95% and power 80%). For better accuracy and avoiding missed data during follow-up, 20% was added to the sample size.

Inclusion criteria were as follows: age of patients were 18–35 years presented by undisturbed tubal EP and fulfilling the inclusion criteria for MTX therapy (maximum gestational sac diameter <3.5 cm, hemodynamic stable, levels of beta-HCG \leq 5000 mIU/ml, no fetal cardiac pulsation, and no evidence of active bleeding or hemoperitoneum) and patients wishing future pregnancy.

Exclusion criteria were any contraindications to MTX (high liver enzymes greater than 2 times of normal, disturbed renal functions (creatinine level >1.5 mg/dl), active peptic ulcer disease, leukopenia less than 3000 cells/ μ l or thrombocytopenia <100,000/ μ l, and known sensitivity to MTX; breastfeeding women; patients with a history of pelvic surgery; patients with ovarian surgery; patients with ovarian masses, for example, endometrioma; patients with poor ovarian reserve; and patients with with any surgical problem contraindicating laparoscopy.

METHODS

Complete history taking included personal, menstrual, obstetrics history, history of tubal EP treated by MTX therapy, previous pelvic operations, ovarian surgery, pelvic inflammatory diseases, and previous EP.

General and local examinations were done to exclude any contraindication for laparoscopy (e.g., morbid obesity).

Diagnosis of EP was done by history, examination, TVS examination (revealing empty uterine cavity and presence of an adnexal mass using a 7.5-MHz transvaginal probe (KAIXIN, KX2000E+, Mindray, China), and serum β -HCG titer on admission and 48 h later.

MTX therapy (two-dose regimen): the patients were treated with two doses (day 0 and day 4) of intramuscular MTX (50 mg/m²). Body surface area (m²) was calculated using the following formula: height (cm)+weight (kg)–60)/100. The levels of beta-GCG levels were measured on days 4 and 7 and another time on days 11 and 14. Success is defined by decreased titer of HCG by greater than or equal to 15% between days 4 and 7. If the desired level of decrease in HCG was obtained, another dose of MTX was given. Monitoring and follow-up of patients were continued on an outpatient basis every week until

beta-hCG levels were below 5 mIU/ml. Hospitalization was indicated if there was abdominal pain, suspected tubal rupture, or if patient is far away from medical services. If the titer did not decrease by the second dose or surgery was required, it was termed failed medical treatment.

Measurement of serum AMH was done using ultrasensitive AMH/MIS ELISA, a quantitative sandwich type immunoassay, before and after three months of MTX therapy.

Measurement of antral follicular count (AFC) was done using a 7.5-MHz transvaginal transducer from day 2 to day 7 of the menstrual cycle. All measurements of AFC were performed by one observer who performed a scan for each ovary from outer to inner margins. All follicles with a diameter of 2–10 mm were measured and counted in each ovary. The total count in both ovaries was labeled as the AFC. A total AFC less than 4 is predictive of poor response and diminished ovarian reserve.

Laparoscopy was done at the postmenstrual phase after sixth months from successful medical treatment of EP. Laparoscopy was done to identify anatomic landmarks and assess any anatomical changes. After the posterior cul-de-sac is filled with irrigation fluid, both adnexa are assessed. The fimbriae were lifted, and the posterior aspect of the ovary and the ovarian fossa were evaluated. The uterus was anteverted, and the uterosacral ligaments, posterior cul-de-sac, and rectum were examined. Tubal patency was assessed by methylene-blue test. Any adhesions were reported.

Ethical approval

An approval from the Ethical Committee of Tanta University was obtained before recruitment. A through explanation of objectives, results, and risks of this study was done for all participants, and a written informed consent was taken from them.

Statistical methods

Statistical analysis of data was conducted using SPSS version 16 (Chicago, Illinois: SPSS Inc, USA). The statistical tests used were mean, SD, and χ^2 test. Standard Student's 't-test' was compared with tabulated one at different levels of significance at the *df*. *P* value less than or equal to 0.05 was considered statistically significant.

RESULTS

A total of 120 cases with ectopic were recruited, but only 56 cases fulfilled the inclusion criteria. Seven cases were initially excluded. The remaining patients (*n* = 49) received MTX as a conservative treatment. At the first follow-up (after 3 months), 13 patients were lost to follow-up. In addition, another 11 cases were lost on the second follow-up at 6 months, with a response rate of 69.4%. Thus, the total number of participants in the analysis of data was 25 cases. These data are presented in Fig. 1.

Clinical criteria of the studied cases

The age of patients ranged between 19 and 35 years, with a mean of 28.24 ± 5.48 years, whereas their average

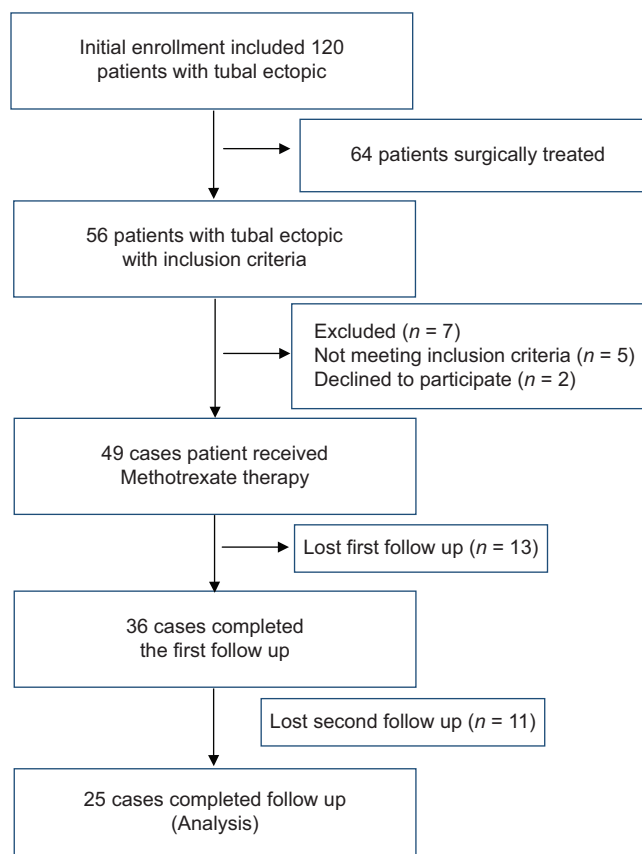


Figure 1: Flow chart of cases during study duration.

BMI was 21.85 ± 4.58 kg/m². Moreover, 24% of patients were PG, as the EP was their 1st pregnancy, whereas 19 cases (76%) were multigravida. According to parity, eight cases (32%) were nullipara, whereas 17 cases (68%) were multipara (Table 1).

Gestational age, initial B-HCG level, and adnexal mass diameter by US

The mean gestational age was 42.6 ± 6.0 days; its range was 28–56 days. Moreover, the mean B-HCG was 1788.48 ± 1171.92 mIU/ml and ranged between 300 and 4115 mIU/ml, whereas the mean adnexal mass diameter was 27.76 ± 9.38 mm and ranged between 10 and 45 mm (Table 2).

Laparoscopic findings after MTX therapy

Regarding tubal patency, 20 cases (80%) had patent ipsilateral tubes, 23 cases (92%) had patent contralateral tubes, five cases (20%) had obstructed ipsilateral tubes, two cases (8%) had obstructed contralateral tubes. Concerning peritubal adhesions, three cases (18.75%) had adhesions in ipsilateral and two cases (12.5%) in contralateral tubes. Moreover, periovarian adhesions were found in two cases (12.5%) in ipsilateral and one case (6.25%) in contralateral side. In addition, fimbrial distortion was present in two cases (12.5%) in ipsilateral and one case (6.25%) in contralateral tubes. Douglas pouch adhesions were found in only one case (6.25%). Regarding tubal patency, patent tubes were found in 13 cases (81.25%)

in ipsilateral and 15 cases (93, 75%) in contralateral tubes. Three cases (18.75%) had obstructed ipsilateral tubes, and one case had (6.25%) obstructed contralateral tubes. These data are present in Table 3.

Comparison between cases with patent tube and cases with blocked tube regarding initial BHCG titer

Fig. 2 shows that the mean initial BHCG in cases with patent tubes was 1752.2 ± 554.36 , whereas in cases with blocked tubes was 2523.75 ± 635.83 mIU/ml. There was a significant difference between the two groups, as the cases with blocked tubes after MTX therapy had initial higher BHCG titer ($P = 0.022$). The Total number of patients in this table is 16, as there were nine (36%) cases that got pregnant before doing laparoscopy.

AMH level before and after MTX therapy

The average serum level of AMH was 3.98 ± 1.11 before MTX therapy and 3.54 ± 1.49 of after that. There is no significant difference between AMH levels before and after therapy ($P = 0.243$) (Fig. 3).

AFC before and after MTX therapy

Table 4 shows that the AFC of the studied cases after treatment was within normal range as 19 cases (76%) had more than eight follicles. There was no significant difference between AFC before and after treatment ($P = 0.251$).

DISCUSSION

EP represents 2% of reported pregnancy according to Centers for Disease Control and Prevention (CDC). Specifically, EP is considered a life-threatening condition. Moreover, the incidence of the maternal deaths owing to the EP is considered to be 9% [1].

MTX remains to be the most used, as well as the most effective, medication in conservative management of EP [2]. The study's results found that MTX had no significant effect on ovarian reserve (Table 4 and Fig. 2). Laparoscopy showed that 81% of affected tubes were patent with no adhesions, 18% of cases had peritubal adhesions, 12% fimbrial distortion, and 6% had Douglas pouch adhesions after MTX therapy (Table 3).

This is the first study to demonstrate the effect of MTX therapy on both pelvic anatomy and ovarian reserve of affected cases.

This is a longitudinal study that evaluates the same cases before and after MTX therapy.

Most similar studies focus on efficacy of MTX therapy and patency of tubes after it; however, few studies discuss ovarian reserve and pregnancy outcomes. The study of Moeller *et al.* [5] followed up cases with EP treated with MTX for a maximum of 10 years and found that the rate of subsequent spontaneous intrauterine pregnancy was 73% after MTX. However, it was 62% after surgery. Moreover, the success rate was 74% after MTX and 87% after surgery. The study found also the recurrence of ectopic was 9.6% after MTX and 17.3% following surgery. The study of Oriol. *et al.* [10], evaluated the effect of MTX when used for treatment of EP following IVF on future reproductive outcome during another IVF trial for the same cases, as well as their effect on ovarian reserve, and they found no statistically significantly difference in the serum AMH levels, peak E2 levels, and number of oocytes retrieved before MTX and after treatment. Moreover, patients had similar

Table 1: Clinical criteria of the studied cases

Age (years)	
Range	19-35
Mean±SD	28.24±5.48
BMI (kg/m ²)	
Range	18.1-25.6
Mean±SD	21.85±4.58
Gravidity	n (%)
PG	6 (24)
MG	19 (76)
Parity	
NP	8 (32)
MP	17 (68)

n=25. MG, multigravida; MP, multipara; NP, nullipara; PG, primigravida.

Table 2: Gestational age, initial B-HCG level and adnexal mass diameter by US

	Range	Mean±SD
B-HCG (mIU/ml)	300-4115	1788.48±1171.92
Gestational age (day)	28-56	42.6±6.0
Adnexal mass diameter (mm)	10-45	27.76±9.38

BHCG, β-human chorionic gonadotropin; US, ultrasound.

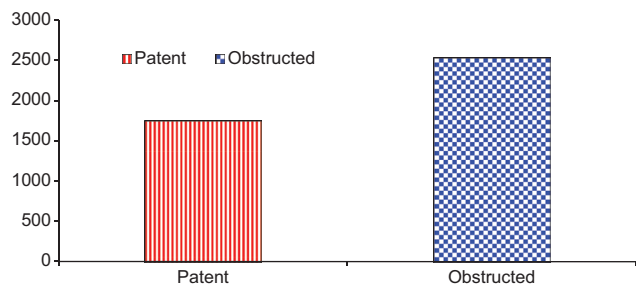


Figure 2: Comparison between cases with patent tube and cases with blocked tube as regard initial BHCG titer.

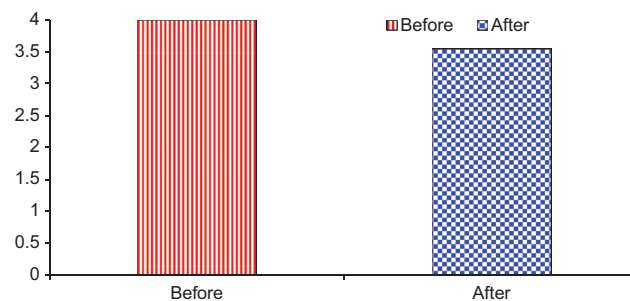


Figure 3: AMH level of the studied cases before and after Methotrexate therapy.

Table 3: Laparoscopic finding after methotrexate therapy

	Ipsilateral [n (%)]	Contralateral [n (%)]
Peritubal adhesion		
Present	3 (18.75)	2 (12.5)
Absent	13 (81.25)	14 (87.5)
Periovarian adhesion		
Present	2 (12.5)	1 (6.25)
Absent	14 (87.5)	15 (93.75)
Fimbrial distortion		
Present	2 (12.5)	1 (6.25)
Absent	14 (87.5)	15 (93.75)
Douglas pouch adhesion		1 (6.25)
Tubal patency		
Patent	13 (81.25)	15 (93.75)
Obstructed	3 (18.75)	1 (6.25)

n=16 because nine patients got pregnant before laparoscopy.

Table 4: AFC of the studied cases before and after methotrexate therapy

AFC	No. of patients before MTX [n (%)]	No. of patients after MTX [n (%)]
<5	1 (4)	2 (8)
5-8	4 (16)	4 (16)
>8	20 (80)	19 (76)
Range	4-19	3-18
Mean±SD	11.12±3.21	10.84±3.88
<i>t</i> -test		1.24
<i>P</i>		0.251

AFC, antral follicle count; MTX, methotrexate.

cycle durations, gonadotropin requirements, and total number of embryos obtained. So, they concluded that in women who are diagnosed with EP, after assisted reproductive technologies, single-dose MTX is safe and does not affect future pregnancy rates. The previous two studies [5,10] are in agreement with our study regarding no harmful effect on ovarian reserve and future reproductive outcome. In the study by Pansky *et al.* [11], tubal patency was investigated by hysterosalpingography in 21 of 37 patients with unruptured tubal pregnancy treated by local MTX injection at laparoscopy. Of the 21 cases, 18 had bilateral tubal patency. They also found that the patient with one tube was also patent. The use of laparoscopy added another step like removal of blood clots and pelvic toilet. In another study done by Prapas *et al.* [12], 20 cases of unruptured ectopic pregnancies were treated with MTX and fulminic acid. The treatment was successful in all but one case. Of 17 cases, six had a normal pregnancy in the 12 months following treatment. Of 20 cases, 17 had tubal patency checked with HSG and laparoscopy.

Fernandez *et al.* [13], treated 100 cases with EP by ultrasound-guided transvaginal injection of MTX. HSG was performed after that for 80 patients. The results of the side of the treated EP revealed a 90% tubal patency rate. The rate of pregnancy was 34 from 58 patients wishing pregnancy.

In a study done by Confino *et al.* [14], 10 women presented with EP, and selective salpingography was performed. The MTX injection results detected seven ampullary pregnancies of 10 patients. The MTX was injected through the selective salpingography catheter and showed complete resolution of EP in seven patients. On hysterosalpingogram performed 3–6 months later, four patients demonstrated patent fallopian tubes.

Tolaymat *et al.* [15], conducted another study to compare MTX treatment versus conservative surgical treatment and their effect on the rates of ipsilateral tubal patency. Women desiring fertility were offered HSG to evaluate tubal patency. HSG was performed for 11 cases treated by linear salpingostomy and 11 cases treated by MTX. Ipsilateral patency was documented in 8 of 11 (72%) tubes treated by linear salpingostomy and 9 of 11 (81%) MTX-treated tubes. One MTX case had a prior ipsilateral ectopic treated by salpingostomy, and two additional cases had a prior contralateral ectopic removed by salpingectomy. Each of these three cases had ipsilateral tubal patency after MTX for the most recent ectopic gestation.

Guyen *et al.* [16], conducted a study on 61 unruptured tubal ectopic pregnancies treated with MTX therapy. A total of 30 patients received multiple doses and 31 patients received a single dose of MTX treatment. At 4–6 months after treatment, the HSG was performed to assess tubal patency. After multiple-dose of MTX, 17 of 30 cases (56.7%) had free passage through the ipsilateral tube. Moreover, 26 of 31 cases (83.9%) had free passage after single-dose MTX therapy. In a study done by Garcia *et al.* [17], 144 patients with EP were treated with systemic MTX. HSG was performed 3 months after that. The HSG show that 72.2% had normal and 18.8% had unilateral obstruction. Overall, 6.3% of tubal patency had defects and 2.8% had bilateral obstruction, and they concluded that HSG is not necessary after medical treatment with MTX, as it does not change the method of treatment in 97.2% of cases. In the study by Al Sayed [18], TVSSG was done to 167 patients after tubal pregnancy treatment. A total of 60 patients were treated with MTX as a single dose and 100 patients had expectant management. The patency of the affected tube was observed by TVSSG. They found that it was 84 and 78%. Ali Abdelhamed *et al.* [19], conducted a study in the College of Medicine, Zagazig University, on 72 women who had unruptured tubal EP. A total of 32 women received MTX and 40 underwent surgery, and HSG was done for cases. They found a 93.8% effectiveness regarding the medical treatment with a single-dose MTX for EP. They also found that in the MTX group when the HSG was done, it showed that 83.3% the ipsilateral diseased tube were open, and the contralateral tubes were patent 93.3%. However, in salpingectomy tube, 82.5% of the contralateral tube was patent.

CONCLUSION

In the management of undisturbed EP, MTX therapy is consider a safe and effective one, with mild adverse effects. Two-dose MTX treatment for EP does not affect the ovarian

reserve regarding serum AMH level and AFC. We recommend medical treatment to be considered before rushing to surgical interference for female patients with EP who fulfil the characteristics for conservative management.

Limitations of this study

The limitation of this study was the restricted time that did not allow for proper follow-up of all cases until getting pregnant and evaluation of fertility outcome. Another limitation of this study is the number of cases that may be relatively less than needed for accurate evaluation.

Acknowledgements

Great thanks to all residents of Obstetrics and Gynecology Department for their great efforts in recruitment and follow-up of patients and gathering data for statistical analysis.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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