The Egyptian Journal of Hospital Medicine (January 2023) Vol. 90, Page 31- 36

The Effect of Surgical Salpingectomy versus Single-Dose Methotrexate on Ovarian Reserve in Ectopic Pregnancy at Alzahraa University Hospital

Rania Mahfouz Abd El-Wahed*[1], Alshaymaa Abdelbadie Abdelalim Nasr[2]
Departments of [1]Obstetrics and Gynecology and
[2]Clinical Pathology, Faculty of Medicine for Girls, Al-Azhar University, Cairo, Egypt
***Corresponding author:** Rania Mahfouz Abd El-Wahed, **Mobile:** (+20) 01001131785, **E-Mail:** rania.mahfouz2@gmail.com

ABSTRACT

Background: Ectopic pregnancy (EP) is a major reason of maternal mortality and morbidity, affecting 1% to 2% of pregnancies. Whether medically with methotrexate (MTX) or surgically with salpingectomy, managing EP could seriously affect female sexuality and reproductive health. The impact of medication and surgical treatment for EP on future fertility is currently unknown and has not been well explored. **Objective:** This study examines the future reproductive effects of medication and surgical management for EP. **Patients and methods:** In this prospective study, 50 EP subjects were involved and randomly subdivided into two groups: (MTX) (*Group A*, n: 25) and salpingectomy (*Group B*, n: 25). Anti-Mullerian hormone (AMH), beta-human chorionic gonadotropin (β-HCG), liver enzyme levels, and platelet count were evaluated before and after the treatment protocol. Hysterosalpingography (HSG) has also been conducted three months after therapy for *Group A* to examine tubal patency. **Results**: Three months following therapy, the AMH levels significantly decreased in *Group A* compared with *Group B* (p=0.04). Also, in *Group A*, AMH levels after 3 months showed a statistically significant decline contrasted with those at the time of therapy. **Conclusion:** AMH levels prior to and after medication with a single dose of systemic MTX and unilateral salpingectomy for EP were positive signs. Present medical and surgical therapy methods have no detectable detrimental impact on ovarian reserve.
Keywords: Salpingectomy, Methotrexate, Ectopic, Pregnancy, Al-Azhar University.

INTRODUCTION

Ectopic pregnancy (EP) is a major reason of death and illness in mothers and affects between 1% and 2% of all pregnant women [1]. Even though it can grow in different places outside of the uterus, the fallopian tubes are the most frequent where it happens. Diagnostic and imaging approaches have improved, making early detection and management possible, leading to a large drop in maternal deaths [2].

Currently available treatments include pharmacological Methotrexate (MTX) and surgical (salpingectomy, salpingostomy, as well as milking) methods. MTX is a potent chemotherapeutic drug that is frequently prescribed for various EPs [3].

However, MTX is considered a highly efficient and non-invasive medication for EP, showing a significant risk of infertility by targeting aggressively dividing cells in the ovaries. Furthermore, MTX therapy is associated with a lengthy period between both the cure of EP and the necessity to wait several weeks before attempting again. There could also be a negative influence on ovarian reserve (OR) [4]. Surgical treatment, such as salpingectomy, is still the best option for EP. Salpingectomy may compromise OR due to the close physical closeness of the fallopian tube and ovary, as well as their shared blood supply [3].

Anti-Müllerian hormone (AMH) is synthesized by granulosa cells of antral follicles in the ovary of females. The hormone is then secreted into the follicular fluid and blood circulation. In health care settings, its concentration in peripheral circulation is monitored. The level of AMH level is commonly associated with the number of primordial follicles, which could make it the most precise hormonal monitor of the OR [5].

AMH levels correlated along with the count of recovered oocytes, the quality of embryos, fertility rates, as well as live birth percentages in patients experiencing in vitro fertilization (IVF) [6]. AMH level is recognized as a more accurate and dependable prognostic of OR, particularly in comparison to conventional markers, including follicle-stimulating hormone (FSH) and antral follicle count (AFC) [7].

Developing the capability of releasing AMH from a primordial follicle is considered to require at least

Received: 02/06/2022
Accepted: 09/08/2022

three months. Due to this, a 90-day interval in AMH levels might be presented to demonstrate significant damage to the primordial follicle pool [8].

Herein, we examined the impacts of the available therapeutic approaches for EP (salpingectomy and MTX) on the OR by estimating AMH levels.

PATIENTS AND METHODS

A prospective, non-randomized controlled clinical trial was carried out at Alzahraa University Hospital .

Ethical approval:

Approval was obtained from the Ethics Committee of the Faculty of Medicine for Girls, Cairo, Al-Azhar University (FMG-IRB) according to the Good Clinical Practice of the ICH, the Helneski declarations, and the World Health Organization guidelines (Clinical Trials ID: 848).

Between December 2018 and September 2021, 50 participants having EP were enrolled in the research. Patients were excluded if they had histories of ovarian surgeries, endometriosis, and chemotherapy which may negatively affect OR, levels of beta-human chorionic gonadotropin b-HCG greater than 3000 mIU/mL, levels of HG less than 10g/dl, levels of platelets less than 150000/ml, elevated liver enzymes and size of the mass is greater than 4 cm by ultrasound or living embryo. Considering the possibility of undiscovered ovarian diseases and physiological changes in the ovarian gland, additional ineligibility factors were a history of infertility and assisted reproductive technology (ART) therapeutic interventions. Moreover, the current clinical trial excluded patients who received multiple dosages of MTX or interventions by surgery, such as salpingostomy.

In this investigation, participants with indications for EP treatment were divided into; *Group A* (MTX only) included 25 patients with undisturbed EP with criteria that allowed single-dose MTX treatment. One systemic dosage of MTX (50 mg/m2) was injected following routine liver and kidney tests, and **human chorionic gonadotropin** (β-hCG) levels were assessed on the fourth, seventh, and fourteenth days of MTX administration. A decline of more than 15% in concentrations was regarded as a satisfactory clinical therapy. Complete blood count (CBC) and liver enzymes were also assessed on the seventh day of MTX treatment, such as serum glutamic pyruvic transaminase (SGPT) and serum glutamic oxaloacetic transaminase (SGOT). Blood levels of AMH blood levels were assessed on the first day and three months following the completion of MTX therapy. A hysterosalpingogram (HSG) was performed for group A three months after the management to assess tubal patency.

Patients who met the exclusion criteria or were unstable in terms of hemodynamics were subsequently allocated to *Group B*. There were 25 subjects in MTX alone (*Group A*) and salpingectomy alone (*Group B*). All participants' demographics (such as age, smoking status, BMI, pregnancy status, and parity) were recorded. Pretreatment and posttreatment AMH concentrations were measured utilizing the Gen II ELISA commercial kit (Beckman Coulter Inc., CA, USA).

Statistical analysis:

The collected data were coded, processed and analyzed using the SPSS (Statistical Package for Social Sciences) version 11 for Windows® (IBM SPSS Inc, Chicago, IL, USA). The Kolmogorov–Smirnov test was utilized to assess the normality of quantitative data. Quantitative data were expressed as mean and standard deviation (SD). Our findings were analyzed using Friedman's two-way ANOVA. We compared the means in normally distributed data employing student t-testing for independent groups and paired t-testing for dependent groups, and we compared the means in non-normally distributed data using Mann-Whitney U test for independent groups and Wilcoxon signed-rank test for dependent groups. P value $\leq$ 0.05 was considered significant.

RESULTS

A total of 50 patients diagnosed with EP were included in this study. Age of the patient, BMI, parity, AMH levels prior to and after treatment, AMH levels, the level of β-HCG, Platelet count, liver enzyme levels, and HSG findings were evaluated in *Group A* (**Tables 1, 2, 3, 4 and 5**). Regarding sociodemographic characteristics, there were no significant differences between the two groups (**Table 1**).

Table (1): The sociodemographic features all participants.

Variable		Group A (n=25)	Group B (n=25)	P-value
Age (years)	**Mean ± SD** **Range**	27.90 ± 6.24 19.0 - 40.0	26.40 ± 4.77 19.0 - 35.0	0.399*
BMI (Kg/m2)	**Mean ± SD** **Range**	28.80 ± 2.82 24.0 - 35.0	27.55 ± 3.47 18.0 - 33.0	0.219*
Parity	**Median (IQR)**	2.0 (0.0 - 1.0)	1.50 (1.0 - 2.5)	0.404╪

*Student T-Test ╪ Mann- Whitney U test

There was a statistically significant decline in β-HCG levels in *Group B* compared to *Group A* on the day of the treatment, the fourth day, and the fourteenth days after the treatment (P values 0.017, 0.025 and 0.001, respectively). At the same time, there were no statistically significant differences in β-HCG levels on the seventh day after treatment. Ultimately, there was a statistically significant decline in β-HCG levels in *Groups A and B* (**Table 2**).

Table (2): Comparison between the two studied groups regarding the level of β-HCG at different times

β-HCG (mUI/mL)		*Group A* (n=25)	*Group B* (n=25)	P-value
Treatment day	**Median (IQR)**	1383.50 (1131.0 - 1835.0)	1098.0 (873.50 - 1287.50)	0.017╪
Day 4	**Mean± SD** **Range**	681.75 ± 168.13 320.0 - 1921.0	467.30 ± 114.43 160.0 - 750.0	0.025*
Day 7	**Median (IQR)**	135.0 (115.0 - 201.0)	115.50 (99.0 - 174.0)	0.061╪
Day 14	**Median (IQR)**	34.0 (19.0 - 46.0)	17.50 (10.0 - 20.0)	<0.001╪
P- value¥		<0.001	<0.001	

β-HCG: Beta-Human chorionic gonadotropin

*Student T-Test, ╪ Mann- Whitney U test, ¥ Friedman's Two-Way ANOVA

Group A, treated with MTX alone, showed a significant decrease in blood platelet counts after 7 days of treatment compared to *Group B*, who was treated surgically (p<0.001). On the other hand, *Group A* was associated with higher levels of AST and ALT after seven days (p<0.001). On the day of therapeutic interventions, the variations in ALT were statistically significant (**Table 3**).

Table (3): Comparisons of platelets count and liver enzymes levels between the two investigated groups at different intervals.

Variable		Group A (n=25)	Group B (n=25)	P-value
Platelets count (×103)				
Treatment day	**Mean ± SD** **Range**	346.68 ± 79.62 212.0 - 488.0	380.95 ± 79.82 155.0 - 494.0	0.114*
Day 7	**Mean± SD** **Range**	162.83 ± 38.54 98.0 - 224.0	277.45 ± 68.65 156.0 - 420.0	**<0.001***
P-value$		<0.001	0.006	
AST level (U/L)				
Treatment day	**Mean± SD** **Range**	23.95 ± 4.68 17.0 - 32.0	21.15 ± 5.24 14.0 - 30.0	0.088*
Day 7	**Median (IQR)**	47.0 (44.0- 50.0)	22.0 (19.50 - 26.0)	**<0.001╪**
P-value#		<0.001	0.012	
ALT level (U/L)				
Treatment day	**Mean± SD** **Range**	23.74 ± 5.75 14.0 - 36.0	28.95 ± 7.11 14.0 - 38.0	**0.020***
Day 7	**Mean± SD** **Range**	48.71 ± 6.75 39.0 - 64.0	30.90 ± 6.43 21.0 - 39.0	**<0.001***
P-value$		<0.001	0.002	

*Student T-Test, ╪ Mann- Whitney U test, $paired t-test, # Wilcoxon signed-rank test.

Three months after treatment, *Group A* showed a statistically significant reduction in AMH levels compared to *Group B* (p=0.04). Furthermore, the decrease in AMH after three months of treatment was statistically significant compared to its levels on the first day of treatment in *Group A* (p<0.001), as shown in table (4).

Table (4): Comparisons of the AMH plasma levels between the two investigated groups at different intervals.

AMH (ng/mL)		Group A (n=25)	Group B (n=25)	P-value
Treatment day	**Median (IQR)**	1.80 (1.55-2.10)	1.94 (1.57-2.36)	0.736╪
After 3 months	**Median (IQR)**	1.24 (1.03-1.90)	1.94 (1.54-2.25)	**0.04**╪
P-value¥		**<0.001**	0.205	

AMH: Anti-Mullerian hormone

╪ Mann- Whitney U test, ¥ Wilcoxon signed-rank test

After follow-up, HSG was performed for group (A). The results showed that one case had left fallopian tube blockage, one had right fallopian tube blockage, and two were missed, as shown in **Table 5**.

Table (5): HSG findings in group A who were treated with MTX

Group A (n=25)			
		N	**%**
HSG	**Missed follow up**	2	8%
	Lt tube blocked	1	4%
	Normal	21	84%
	dilated Rt. Tube	1	4%

HSG: Hysterosalpingography.

DISCUSSION

Even though the frequency of EP has increased since the middle of the 20th century owing to several causes, advances in early diagnosis and intervention have reduced maternal morbidity and mortality [9]. As the present treatment options for EP tend to focus on minimizing mortality and morbidity, fertility maintenance is another major concern for females of reproductive age. In light of the possible consequences of OR, the management of therapeutic methods for these patients can indeed be problematic. Nevertheless, the literature contains contradictory results.

Shirazi *et al.* [10] revealed that single-dose MTX treatment did not reduce ovarian reserve in women with EP. Additionally, **Boots *et al.*** [11] evaluated the effectiveness of a single dosage of MTX on OR after in vitro IVF. They reported that it does not impair OR, responsiveness, or IVF efficiency [11]. There are conflicting reports on the effects of salpingectomy and single or multiple doses of MTX on OR biomarkers, specifically AMH and follicle counts [12].

Before the IVF procedure, a retrospective analysis was carried out in which 198 subjects who underwent either unilateral or bilateral salpingectomy were assessed to determine how salpingectomy affected the OR. This study observed a significant reduction in OR following salpingectomy [13]. However, according to **Lin *et al.*** [14], salpingectomy has no negative effect on OR.

Conventional therapies for different types of cancer in women of reproductive age have revealed dose-dependent reductions in OR [15]. MTX inhibits nucleic acid biosynthesis as well as cellular division and is a widely prescribed chemotherapeutic drug linked to ovary failure at an early age in survivors of childhood cancer [16]. Furthermore, salpingectomy has been implicated to be an adverse influencer on OR, presumably reducing ovarian blood flow [17].

The medical or surgical treatments of tubal EP may impact future fertility by reducing OR. This study compared the effects of single-dose MTX and surgical salpingectomy on OR by measuring AMH levels before and after treatment. Also, HSG was done for the group treated with MTX to assess tubal patency after complete resolution.

In EPs, a salpingectomy is performed, especially if there is evidence of rupture [18]. Salpingectomy requires less serum hCG monitoring than medical care, resulting in fewer hospital visits and venipunctures. Despite the benefits described above, clinicians are concerned that the decreasing blood flow, in combination with the removal of the tube, may impair ovarian function [13].

Sezik *et al.* [17] reported that removing the fallopian tubes in females who underwent a total hysterectomy

with or without bilateral salpingectomy significantly decreased ovarian blood flow. As a result, the vascular arcade of the mesosalpinx is likely to have played a role in the ovarian blood supply. Trophoblast invasion at the fallopian tube increased mesosalpinx blood flow in EP patients [19]. As a result, we hypothesized that ovarian function would be compromised by a sudden decrease in ovarian blood perfusion following EP patients' salpingectomy.

There was no significant difference in AMH levels before and after salpingectomy in this study, similar to the studies mentioned above.

MTX is used to treat EP in carefully selected patients. In this study, we managed EP patients with single-dose MTX with eligibility for MTX to assess its effect on the OR by measuring the level of AMH before treatment and three months after treatment, which showed a statistically significant decrease in the level of AMH before and after treatment. According to **Orvieto *et al.*** [20], FSH, ovarian stimulation features, retrieved oocytes, and AMH concentrations did not alter in IVF patients prior to or after MTX therapy for EP. Before and after MTX administration, there was no variation in AMH, stimulation variables, retrieved oocytes, or the number of embryos in another study, including IVF/ICSI patients [21]. Another study did not report negative effects on OR or ovarian responsiveness in individuals who had EP after an IVF cycle and were treated with MTX [11]. Also, in our study, we compared the effects of salpingectomy versus single-dose MTX on OR by measuring AMH levels before management and three months after, which showed no significant difference between surgical and medical management.

In our study in the MTX group, HSG was performed 3 months after treatment to assess the patency of the fallopian tubes, which revealed that 84% of the patients had normal HSG findings. Only 8% of the patients had abnormal HSG, which was diagnosed by unilateral tubal block, and the second case was diagnosed by a tortuous dilated tube.

Elito *et al.* [22] compared tubal patency after surgery to tubal patency after MTX treatment (as assessed by HSG). Thirty patients received a 50 mg/m2 MTX intramuscular injection, while 35 underwent a salpingostomy operation. Ipsilateral tubal patency was discovered in 84% of MTX-treated patients. In a comparable study, **Guven *et al.*** [23] discovered that tubal patency was 56.7% after repeated doses of MTX and 83.9% after a single dose. Tubal patency was higher, but not statistically significant, in women with a single dose of MTX.

Due to the simplification and consolidation of the trial design, we were unable to conclude the effect of repeated dosages of MTX on OR and reproductive findings contrasted to salpingectomy, which is one of the limitations of the current study.

CONCLUSION

The existing single-dose MTX and unilateral salpingectomy approaches are secure therapeutic strategies for EP that have no discernible negative impact on OR.

Conflict of interest: The authors declare no conflict of interest.

Sources of funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author contribution: Authors contributed equally in the study.

REFERENCES

1. **Rana P, Kazmi I, Singh R *et al.* (2013):** Ectopic pregnancy: a review. Arch Gynecol Obstet., 288(4):747-57.
2. **Khan K, Wojdyla D, Say L *et al.* (2006):** WHO analysis of causes of maternal death: a systematic review. Lancet, 367(9516):1066-74.
3. **de Bennetot M, Rabischong B, Aublet-Cuvelier B *et al.* (2012):** Fertility after tubal ectopic pregnancy: results of a population-based study. Fertil Steril., 98(5):1271-6.
4. **Alexander J, Rouse D, Varner E *et al.* (1996):** Treatment of the small unruptured ectopic pregnancy: a cost analysis of methotrexate versus laparoscopy. Obstet Gynecol., 88(1):123-7.
5. **Meczekalski B, Czyzyk A, Kunicki M *et al.* (2016):** Fertility in women of late reproductive age: the role of serum anti-Müllerian hormone (AMH) levels in its assessment. J Endocrinol Invest., 39(11):1259-65.

6. **Wiweko B, Hanifah N, Sholihah A *et al.* (2018):** Correlation between follicular fluid AMH levels and numbers of oocytes in polycystic ovarian syndrome patients undergoing in vitro fertilization. Journal of Physics: Conference Series, 1073(3):1-5.
7. **Magri F, Schena L, Capelli V *et al.* (2015):** Anti-Mullerian hormone as a predictor of ovarian reserve in ART protocols: the hidden role of thyroid autoimmunity. Reprod Biol Endocrinol., 13(1):106.
8. **Gougeon A (1996):** Regulation of ovarian follicular development in primates: facts and hypotheses. Endocr Rev., 17(2):121-55.
9. **Centers for Disease Control and Prevention (1995):** Ectopic pregnancy--United States, 1990-1992. MMWR Morb Mortal Wkly Rep., 44(3):46-8.
10. **Shirazi M, Pooransari P, Hajiha N *et al.* (2020):** Effect of Single-Dose Methotrexate Treatment on Ovarian Reserve in Women with Ectopic Pregnancy Undergoing Infertility Treatment: A Single-Center Experience. Int J Fertil Steril., 14(1):23-6.
11. **Boots C, Gustofson R, Feinberg E (2013):** Does methotrexate administration for ectopic pregnancy after in vitro fertilization impact ovarian reserve or ovarian responsiveness? Fertil Steril., 100(6):1590-3.
12. **Ulug P, Oner G (2014):.** Evaluation of the effects of single or multiple dose methotrexate administration, salpingectomy on ovarian reserve of rat with the measurement of anti-Müllerian hormone (AMH) levels and histological analysis. Eur J Obstet Gynecol Reprod Biol., 181:205-9.
13. **Ye X, Yang Y, Sun X (2015):** A retrospective analysis of the effect of salpingectomy on serum antiMüllerian hormone level and ovarian reserve. Am J Obstet Gynecol., 212(1):1-10.
14. **Lin Y, Ou Y, Huang F *et al.* (2013):** Ovarian response to gonadotropins in patients with tubal factor infertility: salpingectomy versus nonsalpingectomy. J Minim Invasive Gynecol., 20(5):637-41.
15. **Gracia C, Sammel M, Freeman E *et al.* (2012):** Impact of cancer therapies on ovarian reserve. Fertil Steril., 97(1):134-40.
16. **Lantinga G, Simons A, Kamps W *et al.* (2006):** Imminent ovarian failure in childhood cancer survivors. Eur J Cancer, 42(10):1415-20.
17. **Sezik M, Ozkaya O, Demir F *et al.* (2007):** Total salpingectomy during abdominal hysterectomy: effects on ovarian reserve and ovarian stromal blood flow. J Obstet Gynaecol Res., 33(6):863-9.
18. **Mikhail E, Salemi J, Schickler R *et al.* (2018):** National rates, trends and determinants of inpatient surgical management of tubal ectopic pregnancy in the United States, 1998-2011. J Obstet Gynaecol Res., 44(4):730-8.
19. **Pereira N, Pryor K, Voskuilen-Gonzalez A *et al.* (2017):** Ovarian Response and in Vitro Fertilization Outcomes After Salpingectomy: Does Salpingectomy Indication Matter? J Minim Invasive Gynecol., 24(3):446-54.
20. **Orvieto R, Kruchkovich J, Zohav E *et al.* (2007):** Does methotrexate treatment for ectopic pregnancy influence the patient's performance during a subsequent in vitro fertilization/embryo transfer cycle? Fertil Steril., 88(6):1685-6.
21. **Oriol B, Barrio A, Pacheco A, Serna J *et al.* (2008):** Systemic methotrexate to treat ectopic pregnancy does not affect ovarian reserve. Fertil Steril., 90(5):1579-82.
22. **Elito Junior J, Han K, Camano L (2006):** Tubal patency following surgical and clinical treatment of ectopic pregnancy. Sao Paulo Med J., 124(5):264-6.
23. **Guven E, Dilbaz S, Dilbaz B *et al.* (2007):** Comparison of the effect of single-dose and multiple-dose methotrexate therapy on tubal patency. Fertil Steril., 88(5):1288-92.