Sequential Letrozole and Methotrexate Therapy Safely improved the outcomes of Medical treatment of Tubal Ectopic Pregnancy

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Abstract

Background: Surgical management is curative for tubal ectopic pregnancy (TEP), but multiple studies documented the safety and efficacy of single-dose methotrexate (SD-MTX) as a medical treatment.

Objectives: Evaluation of the success rate (SR) of letrozole (LTZ; 5 mg/day) for 4-day versus SD-MTX (50 mg/m^2) as medical treatment of TEP as judged by the rate of shift-to-surgery.

Patients and Methods: Serum βhCG levels were estimated on D1, 4, 7, 11 and 18 of start of therapies and the extent of change (Δ βhCG) was calculated concerning D-1 levels. For patients of LTZ group, if Δ1-4 βhCG was >10% LTZ therapy was continued, but if it was <10% without TEP disruption, SD-MTX injection was given or salpingectomy was undertaken if TEP was disrupted. Success was defined as TEP resolution as documented by TVU and serum βhCG <15 IU/L within about 19 days of therapy.

Results: SR was significantly higher with LTZ or LTZ/MTX than with SD-MTX and Δ1-4 βhCG was significantly higher with TLZ alone than MTX alone and with MTX alone than the total of LTZ/MTX group. The Δ1-7 βhCG was significantly lower with MTX alone than LTZ alone or LTZ/MTX. Statistical analyses defined age and Δ1-4βhCG as significant predictors for high SR.

Conclusion: Medical treatment for TEP is feasible with SR of 86%; 4-day therapy of LTZ alone provided SR of 62% and 90.6% if supplemented by SD-MTX. The applied policy of using LTZ as a medical treatment for TEP significantly spared the need for MTX and surgery.

Keywords: Tubal ectopic pregnancy; Medical treatment; Letrozole; Methotrexate; Success rate.

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Introduction

Ectopic pregnancy (EP) was defined as the implantation of fertilized ovum anywhere other than the endometrial uterine cavity and accounts for 1-2% of all pregnancies **(Sherer et al, 2023)**, but its prevalence after assisted reproduction trials was found to be higher **(Maher et al, 2024)**.

Tubal EP (TEP) is the commonest and is associated with a high risk of rupture leading to extensive bleeding and complicated surgery, so it represents a significant threat to maternal life **(Wang et al, 2024)**. Management of TEP is still a source of debit where surgical management; salpingotomy or salpingectomy is curative but insufficient removal of the ectopic tissue may occur with salpingotomy causing persistent EP **(Maher et al, 2024)**.

The availability of transvaginal ultrasonography (TVU) and serum β-human chorionic gonadotropin (β-hCG) assay allowed early diagnosis of EP and paved the way for medical treatment of EP, but within certain conditions **(Mirbolouk et al, 2015)**.

Methotrexate (MTX) is an anti-metabolite acting through folic acid antagonism and is most commonly used in cancer chemotherapy **(Weinblatt, 2018)**. However, no dose of MTX is immune against side effects even small doses **(Chande et al, 2014)**. Multiple studies documented the safety and efficacy of single-dose methotrexate (SD-MTX) as a medical treatment for EP that in carefully selected cases might be an effective alternative to surgery **(Sindiani et al, 2020; Lavie et al, 2021; Ray et al, 2022)**. However, the efficacy of SD-MTX is recently questionable and multiple studies tried to evaluate the efficacy of two-dose versus SD-MTX for the medical management of EP **(Tug et al, 2019; Helvacioglu and Dogan, 2021; Khakwani et al, 2022)**.

The Fallopian tube (FT) is a dynamic, steroid-responsive tissue and its epithelium shows cyclic variation across the ovarian cycle under the control of estrogens and progesterone **(Shao et al, 2012)**. Estrogen receptor alpha is the major mediator of cellular estrogenic signaling and is involved in the regulation of FT functions especially enhancement of protein secretion, formation of tubal fluid, and regulation of gamete transport **(Saito and Cui, 2023)**. However, a high estrogens/progesterone ratio has been suggested to disturb embryonic motility in the FT and lead to the development of TEP **(Zhu et al, 2016)**.

Considering the well-defined side effects of MTX, irrespective of the used dosage **(Chande et al, 2014)**, the debit as regards the efficacy of SD-MTX versus double-dose MTX **(Mergenthal et al, 2016)** and the effect of estrogen on embryonic motility and implantation **(Zhu et al, 2016)**; the current study supposed the use of an aromatase inhibitor; letrozole (LTZ) as a 1st line medical treatment of TEP within the same conditions permissible for medical treatment so as to reduce the exposure to MTX with its inherent side effects and raise the success rate of medical treatment whenever it is indicated to spare surgery for complicated or unresponsive cases

The current study aimed to evaluate the outcomes of medical treatment of TEP using sequential administration of LTZ and SD-MTX in case of failure of LTZ as a policy to reduce the exposure to MTX inherent side effects and surgical intervention.

Patients and methods

Design: Prospective comparative interventional study.

Setting: Department of Obstetrics & Gynecology, Faculty of Medicine, Zagazig University.

Ethical considerations: The study protocol was preliminarily approved by the departmental committee before case collection. The study protocol was freely discussed with the couple after assurance of the conditions permissible for application of medical treatment and those agreed to participate were asked to sign the informed consents. After complete case collection, the final approval by the Local Ethical Committee was obtained (#254/24 March 2024) and the study was registered at the clinicaltrials.gov with ID number (NCT06426979).

Patients : Any pregnant patient with lower abdominal pain localized to one side of the pelvis with or without vaginal bleeding was evaluated for enrolment criteria. The collected data included age, marital duration, gravidity, last menstrual period date (LMP), history of contraceptive use, infertility previous abortion or EP. Evaluation of pain criteria including nature, location, and severity of pain and for the presence of associated symptoms as tachycardia, syncope, vomiting, diarrhea, shoulder pain, lower urinary tract symptoms, rectal pressure, or pain with defecation **(Newbatt et al, 2012)**. Then, a general examination was performed to exclude signs of hemodynamic instability that may suggest disturbed TEP as hypotension and tachycardia. Pelvic examination may show tenderness on cervical motion and bimanual examination may allow palpating painful mass lateral to the uterus **(Crochet et al, 2013)**. TVU was performed to ensure the absence of an intrauterine gestational sac, the presence of an intra-tubal gestational sac with or without evident fetal pulsation, competence or rupture of the tube, and the presence of free intra-abdominal bleeding. Blood samples were obtained for the estimation of serum levels of β-hCG to allow therapeutic decision-making.

Inclusion criteria: According to **May et al., (2018)** the inclusion criteria were the presence of gestational masses of <3.5 cm in its greatest diameter in an intact uterine tube and showed no fetal cardiac activity, absence of hemodynamic manifestations or evidence of intra-peritoneal bleeding on TVU and pre-treatment serum hCG of <3500 IU/L.

Exclusion criteria: Any woman presenting with a picture suggestive of TEP and absence of enrollment criteria was excluded from the study

Sample size calculation: Previously, **Alsammani & Moona, (2016)** retrospectively evaluated the success rate of MTX as a medical treatment for TEP through the outcomes of 109 patients and **Kim et al, (2017)** prospectively detected insignificant differences in the success rate of SD-MTX versus double-dose MTX used by 52 and 35 patients, respectively. Using the G*Power (Version 3.1.9.2) **(Faul et al, 2007)**, the sample size that was calculated to provide a study power of 80% using α-error 5%, and considering the effect size of 0.20 by the F test model defined 100 patients per group is the suitable number to ensure the certainty of the null hypothesis that the use of the sequential LTZ-MTX therapy will provide a success rate better than SD-MTX even if the difference is insignificant.

Randomization & Grouping : Using a computer-generated random number sequence in a 1:1 ratio with the dropping of odd numbers, patients were categorized into two groups; Group MTX (Control group) and Group LTZ-MTX (Study group). Group titles were printed into cards that were enclosed in sealed envelopes

and patients were asked to choose a closed envelope.

Medications

1. **Letrozole** (FEMARA 2.5 mg tablets; 30 film-coated tablets; Novartis) two tablets daily
2. **Methotrexate** (TREXAN; Methotrexate 25 mg/ml; Orion Corporation; Orion Pharma; Finland) was given as single-dose of intramuscular (IM) injection in a dose of 50 mg/m^2.

Tools for decision-taking

1- TVU: all the enrolled women underwent TVU for assessment of their clinical status and managed according to the Green-top Guideline No. 21 RCOG/AEPU Joint Guideline; Nov 2016 **(Elson et al, 2016)** as follows:

- Women had disrupted TEP with hemoperitoneum or showed fetal pulsation and have healthy contralateral tube underwent laparoscopic salpingectomy, while for women with a history of fertility-reducing factors as previous EP, contralateral tubal damage, previous abdominal surgery, previous pelvic inflammatory disease, laparoscopic salpingotomy was performed
- Women with intact TEP and were free of TVU manifestations of hemoperitoneum and clinical manifestations of hemodynamic instability were enrolled in the study for trial of medical treatment

2- Estimated serum levels of βhCG:

- At time of enrolment women had serum βhCG level of >3500 IU/L were shifted to surgery according to the previous guidelines. Women had serum βhCG of <3500 IU/L were enrolled in the study to receive either LTZ 5 mg as 4-day therapy (Study group) or MTX as single dose IM injection of 50 mg/m^2 (Control group).
- On Day-4 of therapy, serum βhCG levels were estimated for all patients. If serum βhCG levels were decreased by >10% of the baseline level (D1 level) before start of treatment; i.e. Δ1-4 is >10%, in women of the study group, LTZ therapy was continued.
- On Day-7 of therapy, serum βhCG levels were estimated for all patients. If serum βhCG level was decreased by >15% between days 4 and 7; i.e. Δ4-7 >15%, βhCG levels were then measured weekly until it is <15 IU/L
- In case of failure of women of study group to achieve a Δ1-4 of >10%, SD-MTX was given and βhCG levels were estimated on the 11th day to judge for the percentage of decrease.
- In case of failure to achieve TEP resolution as documented by TVU and serum βhCG <15 IU/L within about 19 days of therapy **(Helmy et al, 2015)**, or increasing serum βhCG levels, development of clinical or laboratory and ultrasound signs of intra-abdominal bleeding, TVU was performed to assure the disruption and surgical intervention was undertaken according to the previous guidelines

Study outcomes

1. The primary outcome is the success rate (SR) of the trial of LTZ therapy as defined by the number of TEP patients who achieved resolution of TEP that was assured by TVU and serum hCG≤ 15 IU/L without the need for shift to surgery or MXT.
2. The secondary outcome is the overall SR of medical treatment as defined by the progressive

decrease of serum hCG without need for urgent surgical intervention

Statistical analysis

The significance of the Δ βhCG for each group was evaluated using the paired t-test, while the difference between groups was assessed using the One-way ANOVA and Chi-square tests. The relation between the SR and patients' data and Δ1-4 βhCG was performed using Pearson's correlation analysis. The Receiver Operating Characteristic (ROC) curve analysis was used to determine the significant predictors for SR as judged by the significance of area under the ROC curve (AUC) in relation to the area under the reference line (=0.05) and the predictors were verified using the Multivariate Regression analysis to determine the persistently significant predictors. The optimum cut off point for significance was P<0.05. Statistical analyses were conveyed using IBM® SPSS® Statistics software (Version 22, 2015; Armonk, USA)

Results

Throughout 2-year duration, 231 women presented by history of missed period and clinical manifestations of TEP, 23 patients showed manifestations of disturbed TEP that was assured by TVU, 5 women had serum βhCG >3500 IU/L and 3 women showed fetal cardiac pulsation in a TEP with high serum βhCG level, these 31 patients underwent urgent laparoscopic exploration and had salpingectomy. The remaining 200 women who fulfilled the inclusion criteria were randomly divided into two equal groups (n=100 patients). Patients' enrolment data showed insignificant differences between both groups (**Table.1**).

Table 1. Patients data

Clinical data		**MTX**	**LTZ/MTX**	**P value**
Age (Years)		28.5±4.2	27.3±4.5	0.054
BMI (kg/m^2)		32.6±4.5	32.9±2.4	0.183
Duration of marriage (Y)		2.8±1	2.7±0.7	0.406
Gravidity	**G1:G2:G3**	15:44:41	18:48:34	0.577
Parity	**P0:P1:P3**	33:55:12	27:57:16	0.546
Previous EP		3 (3%)	4 (4%)	0.700
History of infertility		5 (5%)	3 (3%)	0.471
History of contraception		2 (2%)	7 (7%)	0.088
Mode of getting pregnant	**Normal**	99 (99%)	98 (98%)	0.561
	ART	1 (1%)	2 (2%)	
Last menstrual period (days)		42.4±6.5	41.8±5.9	0.494
Presenting manifestations	**Pain**	87 (87%)	79 (79%)	0.132
	Vomiting	26 (26%)	38 (38%)	0.068
	Diarrhea	8 (8%)	12 (12%)	0.346
	Shoulder pain	4 (4%)	3 (3%)	0.700
	Rectal pressure	2 (2%)	3 (3%)	0.651
	Pain with defecation	2 (2%)	5 (5%)	0.248
	Lower urinary tract symptoms	5 (5%)	3 (3%)	0.471
	Symptom/patient	1.3	1.4	

Regarding the progress of patients who received LTZ; during the 1st 4-days of therapy, the Δ1-4 βhCG was >10% in samples of 64 patients who were continued to receive LTZ alone, but during follow-up two patients had disturbed TEP and were admitted for emergency salpingectomy. Fortunately, the remaining 62 patients had continued on LTZ therapy alone till resolution of their TEP giving a success rate of 62% for LTZ alone as a medical treatment of TEP. As regards the remaining 36 patients, the Δ1-4 βhCG was <10% and four of them developed clinical and TVU manifestations of disturbed TEP and underwent emergency laparoscopic salpingectomy, while 32 patients received SD-MTX in addition to LTZ therapy. Unfortunately, three patients developed tubal disruption during 4-11 day follow-up and were admitted for emergency salpingectomy, while 29 patients continued their follow-up uneventfully till resolution of their TEP giving the combined LTZ and MTX a success rate of 90.6%.

On the other hand, 12 patients of MTX group had Δ1-4 βhCG of <10% and developed manifestations of tubal disruption, so were shifted to surgery, while 88 patients had Δ1-4 of serum βhCG of >10% and continued follow-up. During the 4-11 follow-up period, seven of these patients required surgical intervention and 81 patients continued follow-up uneventfully till resolution of their TEP, so the total success rate of MTX alone was 81% (**Fig.1**).

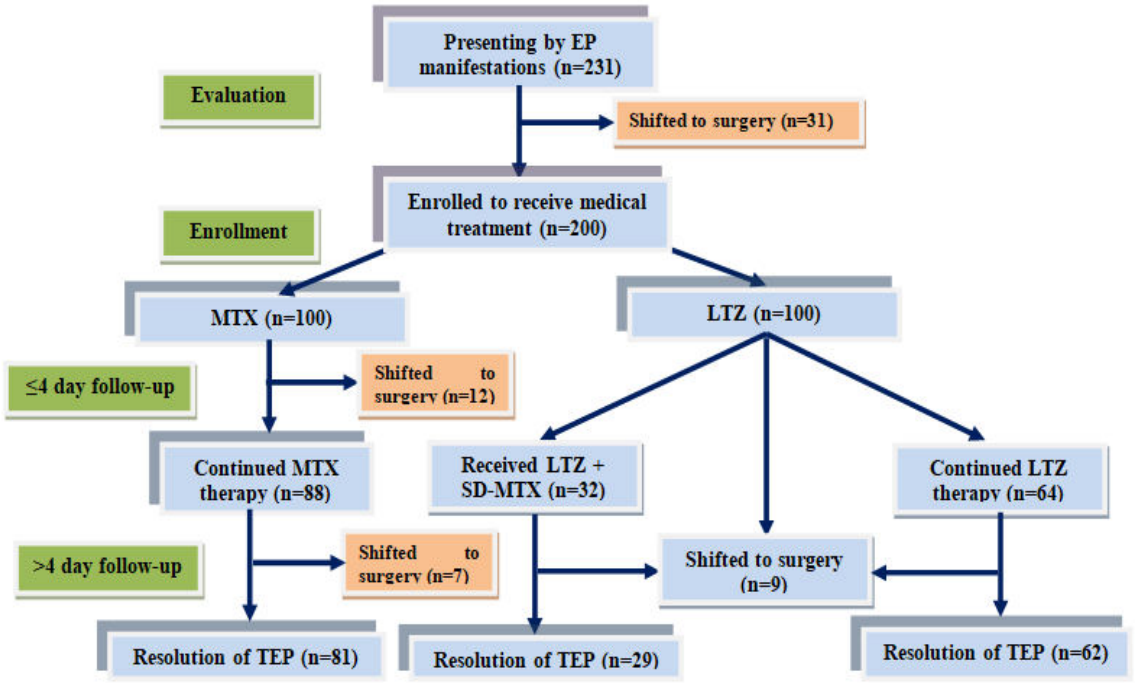

Fig.1. Study flow chart

Collectively, the SR for MTX alone was 81% and for LTZ alone was 62%, while the SR of the sequential LTZ/MTX therapy was 90.6%. Considering the complete TEP resolution rate as a success of medical treatment, the TEP resolution rate in LTZ/MTX group was significantly (P=0.041) higher than that of MTX group (90.6% vs. 81%, respectively) as shown in (**Fig. 2**).

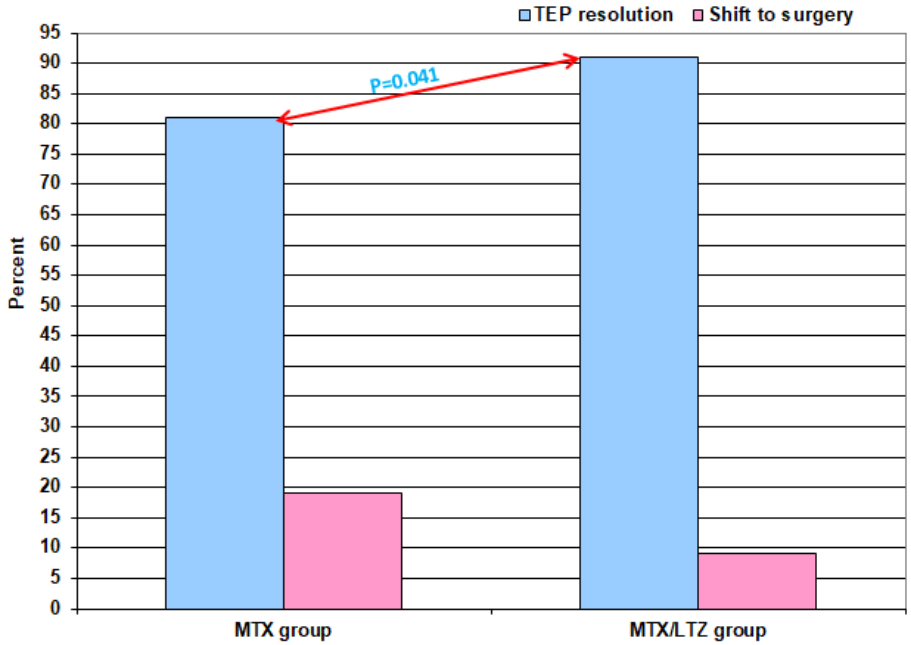

Fig.2. Distribution of women of both groups according to the TEP resolution rate "success rate of medical treatment"

Mean level of estimated serum βhCG showed time-dependent decline in all patients. Levels estimated in D4-samples were significantly lower in responders to LTZ alone than responders to MTX alone (P=0.004) and in samples of patients of MTX group than in samples of total LTZ/MTX group. Subsequently, the Δ1-4 was significantly highest in patients received TLZ alone than those received MTX alone (P=0.0022) and in patients of MTX group than total patients of LTZ/MTX group (P=0.0002). On contrary, serum βhCG levels estimated in samples of D7 were significantly lower in patients received TLZ alone (P=0.00001) and total patients of LTZ/MTX group (P=0.0002) in comparison to levels estimated in samples of patients of MTX group. Similarly, the Δ1-7 in samples of patients received MTX alone was significantly (P<0.001) lower than that calculated in samples of patients received LTZ alone and total patients of LTZ/MTX group. However, levels estimated in samples of D11 and D18 showed insignificant differences between all patients despite being lower in patients received LTZ alone (**Table.2**).

Table 2. Time-course hCG kinetics through 18-day follow-up of the enrolled patients

Variables		MTX group (n=81)	LTZ/MTX group (n=91)	P1	Responder to LTZ alone (n=62)	P2
D1		3080.7±177.8	3134.3±213.8	0.079	3057.7±205.3	0.474
D4		2163±261.7	2325.8±537.5	0.014	2018.6±328.7	0.004
Δ1-4	**Mean**	29.8±7.3	26.3±14	0.0002	34.1±9.2	0.0022
	Range	13.4-42.7	7.7-49.5		12.7-49.5	
D7		1003.9±117.8	952.5±146.6	0.013	909.9±130.5	0.00001
Δ1-7	**Mean**	66.9±4.2	69.6±4	<0.001	70.2±3.7	<0.001
	Range	50.7-75.2	60-79.4		60.9-79.4	
D11		514.6±109.4	498±108.7	0.319	482.9±101.6	0.078
Δ1-	**Mean**	82.3±3.4	84.2±3.3	0.091	84.2±3.1	0.096

11	**Range**	73.4-90.5	74.2-90.6		74.2-90.6	
D18		217±62	200.5±50.9	0.058	201.3±50.8	0.108
Δ1-18	**Mean**	93±1.9	93.6±1.6	0.062	93.4±1.6	0.119
	Range	86.7-97	87.9-97.1		87.9-96.3	

P1: Significance of difference between MTX and LTZ groups; P2: Significance of difference between responders to MTX alone and LTZ alone; P3: Significance of difference between responders to MTX alone and to LTZ/MTX

Pearson's correlation analysis showed positive significant correlation between the success of medical treatment with Δ1-4βhCG and parity, while showed negative significant correlation with maternal age and BMI, but positive insignificant correlation with gestational age. ROC curve analysis also excluded gestational age as a predictor for success and showed insignificant AUC for parity, while suggested that high Δ1-4βhCG is the significant positive predictor, while old age and high BMI as significant negative predictors for success of medical treatment (**Fig. 3**). Regression analysis of these three predictors excluded BMI in one model and in the second model assured that high Δ1-4βhCG and age are the persistent significant predictors for success of medical treatment (**Table.3**).

Table 3. Statistical analyses for the predictors of success of medical treatment

Analysis Variates	**Correlation**		**Receiver Operating Characteristic curve**				**Multivariate Regression**			
	"r"	**P**	**AUC**	**Std.**	**P**	**95% CI**	**Model**		**β**	**P**
Age	-0.264	<0.001	0.289	0.051	<0.001	0.188-0.390	1	Age	-0.253	<0.001
BMI	-0.267	<0.001	0.266	0.055	<0.001	0.159-0.373		BMI	-0.179	0.007
Parity	0.140	0.048	0.597	0.051	0.094	0.496-0.698		Δ1-4βhCG	0.296	<0.001
GA	0.129	0.069	Excluded				2	Age	-0.286	<0.001
Δ1-4βhCG	0.305	<0.001	0.765	0.039	<0.001	0.689-0.840		Δ1-4βhCG	0.324	<0.001

BMI: Body mass index; GA: Gestational age; "r": Pearson's correlation coefficient; AUC: Area under curve; Std. Standard error; CI: Confidence interval

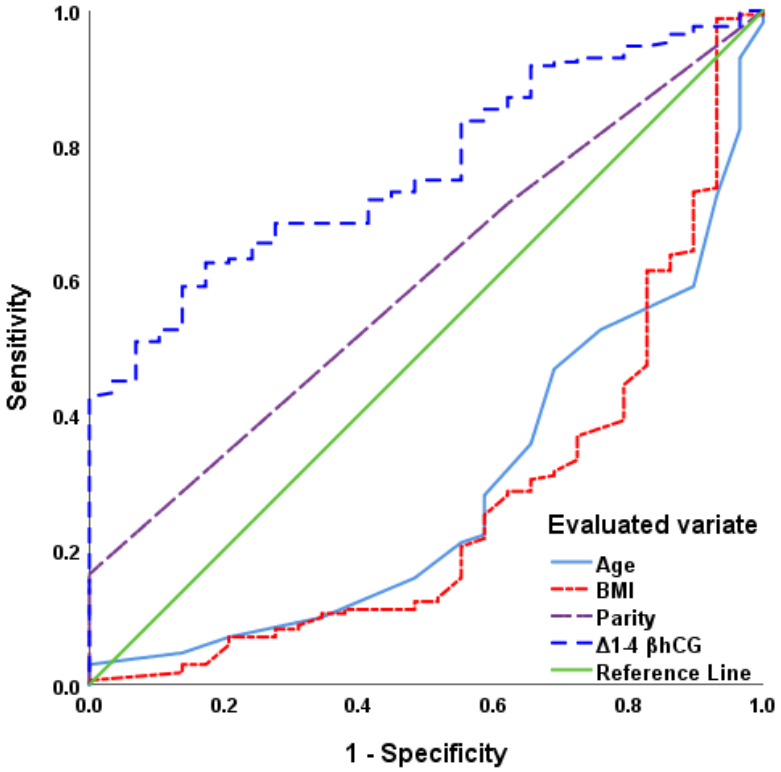

Fig. 3: ROC analysis of patients' data and Δ1-4 βhCG as predictors for the success of medical treatment for TEP

Discussion

During this study 28 women (14%) required surgical interference, 19 of patients received SD-MTX only and 9 patients of those received LTZ or LTZ/MTX, thus using LTZ as medical management for TEP alone or as the applied protocol for sequential LTZ-TMX therapy significantly (P=0.041) reduced the need for surgical intervention (90.6% versus 81%). Sixteen cases were operated up on during the duration of 1-4 days of therapy and 12 patients during 4-11 day of therapy. Almost of patients had surgery during 1-4 days showed weak response to medical treatment and showed <10 Δ1-4 βhCG. Unfortunately, Δ1-4 βhCG for patients had surgery during 4-7 days was >10%, thus, serum βhCG levels might not be a solid predictor for outcome. Correlation analysis defined negative relation of the success of medical treatment with patients' age and BMI, but positive significant correlation with Δ1-4βhCG and statistical analyses defined age and Δ1-4βhCG as highly significant predictors for success of medical treatment.

The reported surgical-shift rate (14%) goes in hand with the previously reported rates, 12% **(Mathlouthi et al, 2013)**, 13.9% **(Goh et al, 2020)** and 26.4% **(Hamish et al, 2020),** during SD-MTX medical therapy. Moreover, **Beguin et al., (2020)** detected surgical interference rate of 20% during SD-MXT and attributed this to pain, increased mass size and suboptimal hCG kinetics. Also, **Helvacioglu & Dogan (2021)** reported 16% failure rate for double-dose MXT. Recently, **Zhou et al., (2023)** and **Aiob et al., (2023)** reported surgical interference rates of 15.7% and 15.1% for women who received SD-MXT for TEP. Interestingly, **Gingold et al., (2021)** found initial MTX therapy for TEP did not exclude the need for surgery but can postpone it. The reported success rate for MTX alone (81%) was superior to that reported by other studies evaluated MTX therapy for

TEP; 66.6% **(Levin et al, 2020)**, 77.53% **(Lin et al, 2021)** and 77.2% **(Yildiz and Bilge, 2023)**.

In hand with the detected relation between patients' data and success of medical treatment, **Levin et al., (2020)** reported insignificantly lower success rate in obese than normal weight women who received MTX for TEP and **Lin et al., (2021)** detected negative significant relation between serum βhCG levels and patients' age and success of MTX therapy. Recently, **Aiob et al., (2023)** found failure of medical treatment was positively correlated with parity, advanced pregnancy age and high serum βhCG levels. Also, **Buhur & Unal (2023)** reported positive relation between gestational ages and need for surgical intervention for TEP women and attributed this to increased diameter of the ectopic focus with increased β-hCG values.

The trail using LTZ 5 mg/day for 4-days resulted in weak reduction of serum βhCG in 36 patients; 4 patients showed aggravation of clinical symptoms and underwent surgery, while for the remaining 32 patients LTZ was supplemented by SD-MTZ. During D4-11follow-up, three patients required surgical intervention for persistently weak response and 29 patients had TEP resolution. The remaining 64 patients showed β-hCG Δ1-4 of >10% and continued LTZ therapy that resulted in progressive decline of serum βhCG levels and increased Δ4-7 and Δ7-11, but two patients showed manifestations of disturbed TEP and underwent urgent laparoscopy. The remaining 62 patients showed complete TEP resolutions as evidenced by weekly TVU and estimation of serum βhCG, giving LTZ 62% success rate as a sole therapy for TEP.

Review of literature detected scarce studies used LTZ for TEP medical management, **Mitwally et al., (2020)** reported 86% success rate for both LTZ and MTX and concluded that the reported high resolution rate and better safety profile with LTZ in comparison to MTX might allow its application for TEP management. However, this high success rate may be attributed to the small sample size and to the non-randomization that may allow patients with low βhCG to be included in LTZ group, thus arousing suspicion of this high success rate. Similarly, **Auger et al., (2020)** criticized the results obtained by **Mitwally et al., (2020)** for the same points and assured the drawback of non-randomization where patients of LTZ arm were found to have lower baseline βhCG levels than patients of MTX group (1065 vs. 1415 IU/L).

Also, **Rezaei et al., (2021)** tried LTZ versus placebo with SD-MTX in both arms for treatment of 90 TEP patients and reported minor increase in β-hCG levels in D4 samples of patients received placebo, but levels decreased progressively on D7 and D14 samples, while in LTZ group β-hCG levels had decreased since D1 progressively to D14 with insignificant differences between both groups as regards the need for further surgery or second-dose of MTX. However, this study was criticized for multiple points; firstly, the mean value of D1 serum β-hCG level was 696.3 IU/L which is an important point where **van Mello et al., (2018)** had documented that many early ectopic pregnancies with low β-hCG levels may resolve spontaneously without treatment, so some of the reported LTZ success might not be related to its effect. Secondly, this study alleged that there was no need for surgical interference for any case, despite documenting in the study consort that 7 cases of each group were excluded for emergency surgery and

thus the sample size was reduced to 76 and the success rate may be faked.

Thereafter, **Alabiad et al. (2022)** reported TEP resolution rates of 65% and 85% after 11-d LTZ therapy using low-dose (5 mg) and high-dose (10 mg), respectively. The reported TEP resolution rate with low-dose LTZ coincided with ours rate. However, one point of difference was that the current study reported starting resolution on D4 of therapy and on continuation of LTZ therapy no case required surgical intervention or administration of MTX, while **Alabiad et al. (2022)** converted cases that did not show TEP resolution to surgery after 11-day therapy and this may expose these women to the risk of tubal rupture. Another limitation of this study was the small sample size that was 20 patients per group that may induce bias of the significance of the results. Also, comparison of resolution rate and level of βhCG in cases received LTZ versus those underwent surgery from the start resulted in high significance of difference between the three groups, despite the authors' documentation of the insignificant difference (P=0.144) between both study groups and attributed this to the small sample size.

Review of literature pointed to a role of caspase-3 activated apoptosis as the most probable mechanism for TEP resolution with LTZ therapy, where **Silveira et al., (2022)** using LTZ exposed human cumulus cells detected significant reduction of the percentage of cells in the S-phase whenever DNA replication and repair occurs with disruption of the cell cycle in comparison to control unexposed cells. **Alabiad et al. (2022)** using immunohistochemistry detected significantly higher placental apoptotic index cleaved caspase-3 in women had salpingectomy after failure of LTZ therapy than those had surgery without previous LTZ therapy and attributed the effect of LTZ to the initiation of placental tissue apoptosis. Thereafter, **Ajibare et al. (2023)** using animal model of LTZ-induced PCOS detected overexpression of genes of caspase-3, interleukin-1β and tumor necrosis factor–α than in control animals. Recently, **Alabiad et al. (2024)** using pregnant animal found high-dose LTZ for 10-days during pregnancy caused significantly higher embryonic mortality, post-implantation loss rate and apoptotic index of cleaved caspase-3, while reduced placental weights with down-expression of growth factor.

Conclusion

Medical treatment for TEP is feasible and successful by a rate of 86% whenever proper patients' selection was fulfilled. LTZ alone as a preliminary trial as 4-day therapy provided SR of 62% and in case of failure to achieve sufficiently lower levels of Δ1-4 βhCG, it allowed higher SR if supplemented by MTX of 90.6%. The applied policy of using LTZ as medical treatment for TEP significantly spared the need for MTX and surgery.

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