

### ***Outcome of Laparoscopic Management of undisturbed Ectopic Pregnancy versus Medical Management***

#### **Abstract**

**Background:** Ectopic pregnancy (EP) is major health problem that women experience during reproductive years. The most frequent type of EP is tubal pregnancy, while non-tubal and heterotopic extra-uterine pregnancies are rare. Recently; ectopic pregnancy can be diagnosed before patient's clinical state is worsened.

**Aim:** was to compare outcome of laparoscopic therapy of undisturbed adenexial ectopic pregnancy versus medical therapy by methotrexate.

**Methods:** This randomized controlled clinical study on 50 patients attending outpatient clinic and inpatient at Department of Obstetrics and Gynecology -Tanta University Hospital. The study participants included women who underwent laparoscopy or underwent medical therapy with MTX for undisturbed adenexial ectopic pregnancy. We analyzed data of 50 women 25 treated with single dose MTX and 25 cases treated with laparoscopy for undisturbed adenexial ectopic pregnancy between 2020 and 2021. Success of treatment in laparoscopy group was defined as significant decrease in one week post-therapeutic quantitative  $\beta$ -HCG, while in MTX group success of treatment was defined as decrease in BHCG level more than 15% between day 4 and day 7, with no need for surgical intervention..

**Results:** Success of treatment in laparoscopy group (23 cases, 92%) and (18 cases, 72%) in methotrexate group, no statistically significant difference between two groups ( $p=0.306$ ). In methotrexate group the 7 cases who had failed medical therapy, underwent laparoscopy. There was no statistically significant difference between the two groups regarding persistent trophoblast ( $p=0.490$ ), as two (8%) cases in laparoscopy group, while no cases in methotrexate group.

**Conclusions:** Laparoscopic surgery is as effective as methotrexate therapy for conservative therapy of undisturbed adenexial ectopic pregnancy and methotrexate has advantage of being non-invasive procedure.

**Keywords:** Ectopic pregnancy, Methotrexate, Salpingostomy.

## Introduction

Ectopic pregnancy (EP) is major health problem that women experience during reproductive years. EP is developed when a blastocyst is abnormally implanted outside uterine cavity endometrium. The most frequent type of EP is tubal pregnancy, while non-tubal and heterotopic extra-uterine pregnancies are rare. <sup>(1)</sup>

E.P can also be located in the ovary, in uterine horn, in uterine cervix, in cesarean section scar, and in abdominal region. Heterotopic pregnancy and non- tubal pregnancy are difficult to be diagnosed and managed, and they are associated with higher morbidity<sup>(2)</sup>. EP is one of the most prevalent causes of maternal morbidity and mortality. Even today, it results in about 6% of pregnancy-associated mortality. <sup>(2,3)</sup>Recently; ectopic pregnancy can be diagnosed before patient's clinical state is worsened, so it turned into more benign health problem. Diagnostic trans-vaginal ultrasound and human chorionic gonadotropin (HCG) level are cornerstone of diagnosis.<sup>(4)</sup> But it is a common mistake to perform Trans-vaginal ultrasound alone, because the adnexa might be located at higher level, and only pelvic abdominal ultrasound can give suggestive image that can diagnose Ectopic Pregnancy. <sup>(5)</sup>

Ectopic pregnancy should be suspected, if a gestational mass is detected by ultrasonography in adenexial region with absence of any signs of intrauterine pregnancy. Yolk sac or fetal pole appearance in the ectopic adenexial mass verifies diagnosis of ectopic pregnancy. A pseudo-gestational sac can be identified by presence of little fluid collection in the uterine cavity. <sup>(3)</sup>

Proper early diagnosis of E.P provides us adequate time to evaluate different treatment options and choice of proper management. This is important not only for success of EP management (E.P removal) which is a narrow aim but also remaining optimal fertility in women who desire future pregnancy. <sup>(6)</sup>

Available therapeutic options for Ectopic Pregnancy are expectant management, medical therapy and surgery. Expectant management is based on the fact that early ectopic pregnancy is a self-limiting process in many cases that end in tubal abortion or ectopic pregnancy re-absorption. <sup>(6)</sup>

Also MTX administration has an acceptance in many cases. <sup>(6)</sup> Methotrexate , an immunosuppressive drug, is a folic antagonist that inhibits DNA , RNA and protein synthesis, so causing cell death<sup>(7)</sup>. Low-dose methotrexate treatment protocol which introduced 20 years ago is the treatment of choice for ectopic pregnancy when

possible. <sup>(8)</sup> After conservative surgical management, systemic MTX treatment and expectant management, Persistent trophoblastic disease may be recognized as a complication, which can lead to clinical symptoms returning and require an additional therapy. <sup>(6)</sup>

According to the Food and Drug Administration; women should avoid pregnancy after medical therapy by MTX for at least one ovulatory cycle. <sup>(9)</sup> Laparoscopy is the most accepted approach for haemodynamically stable patients, while laparotomy is more suitable for haemodynamically unstable cases. <sup>(10)</sup> The decision to perform salpingostomy or salpingectomy for the treatment of tubal E.P should depend on the clinical status of the patient, degree of fallopian tube damage and patient's desire for future pregnancy. <sup>(11)</sup>

## PATIENTS AND METHODS

**Study design:** randomized controlled clinical study on 50 patients attending outpatient clinic and inpatient at Department of Obstetrics and Gynecology -Tanta University Hospital from March 2020 till October 2021. 50 cases were diagnosed with undisturbed adnexial ectopic pregnancy and were eligible for randomization; 25 cases in each study group.

- Our patients were selected according to the following inclusion criteria: Age (20-35 years), undisturbed adnexial ectopic pregnancy, haemodynamically stable, ectopic mass size not more than 4cm at its greatest dimension, quantitative B-HCG level is less than 5000 m.IU/mL, **and exclusion criteria: were** disturbed ectopic pregnancy, coexistent viable intrauterine pregnancy, haematological, renal or hepatic impairment, breast feeding, hypersensitivity to methotrexate, immunodeficiency or concurrent use of corticosteroids, cardiac pulsation on fetal pole of ectopic pregnancy. All participants signed a written consent after clarification of the purpose of the study, interventions, outcome and possible complications. All patients in the study subjected to full history taking including complete medical and surgical history, general examination, abdominal and vaginal examination, investigations included: (Quantitative  $\beta$ -HCG, serum creatinine, liver function, Rh, and CBC) and trans vaginal ultrasound. **Only with group A;** Laparoscopic intervention such as: tubal aspiration, salpingostomy, salpingectomy, and ovariectomy in which embryonic tissue only removed with preserving the ovary. **Only with Group B :** according to Lipscomb2012(single dose protocol), the following had done ;on **Day (0)** quantitative  $\beta$ -HCG level was measured, on **Day (1)** intramuscular

administration of single-dose of methotrexate (50 mg/m<sup>2</sup>) .on **Day (4)** quantitative  $\beta$ -HCG level was detected, If the  $\beta$ -HCG level had dropped 15% or more; Successful treatment was occurred, weekly  $\beta$ -HCG level was measured until it became undetectable, but if decrease of  $\beta$ -HCG level was less than 15%, 2<sup>nd</sup> dose methotrexate was given (maximum doses is 3 doses) then quantitative  $\beta$ -HCG was measured on **Day (7)**; If was not decreased, laparoscopic intervention had performed. Patients have been followed 3 months after medical or laparoscopic therapy to detect outcome and Histo-salpingo-gram was done if not get pregnant when cases desire pregnancy. **Outcome:** was detected such as: success of treatment, tubal integrity, occurrence of normal pregnancy, recurrence of ectopic pregnancy, complications of treatment.

**Statistical analysis:** The collected data were tabulated, and statistically analyzed using SPSS program (Statistical Package for Social Sciences) software version 26.0, Microsoft Excel 2016 and MedCalc program software version 19.1. Descriptive statistics were done for numerical parametric data as mean  $\pm$ SD (standard deviation) and minimum & maximum of the range and for numerical non parametric data as median and 1<sup>st</sup> & 3<sup>rd</sup> inter-quartile range, while they were done for categorical data as number and percentage. Inferential analyses were done for quantitative variables using independent t-test in cases of two independent groups with parametric data and Mann Whitney U in cases of two independent groups with non-parametric data. Inferential analyses were done for qualitative data using Chi square test for independent groups. The level of significance was taken at P value <0.05 is significant, otherwise is non-significant. The p-value is a statistical measure for the probability that the results observed in a study could have occurred by chance.

**Results:** The demographic characteristics (age, gravidity and parity) for all study cases are given in Table 1 and clinical characteristics (side of ectopic mass, history of previous ectopic pregnancy, history of previous spontaneous abortion and PID) in Table 2. There were no significant differences between the two study groups in these baseline characteristics.

**Table (1):** Comparison between the two studied groups as regards demographic characteristics.

		Group A (Laparoscopy group) (n = 25)		Group B (Methotrexate group) (n = 25)		Test value	P-value
		n	%	n	%		
Age (years)	Range	20.0- 35.0		20.0- 35.0		T= 1.697	0.096
	Mean± SD	29.12± 4.91		26.72± 5.09			
	Median	30.0		25.0			
Gravidity	Range	1.0- 5.0		1.0- 5.0		zMWU= 1.72	0.085
	Mean± SD	3.4± 1.2		2.8± 1.2			
	Median	3.0		3.0			
	G1	3	12.0%	4	16.0%	X <sup>2</sup> = 8.54	0.074
	G2	1	4.0%	8	32.0%		
	G3	10	40.0%	5	20.0%		
	G4	6	24.0%	6	24.0%		
G5	5	20.0%	2	8.0%			
Parity	Range	0.0- 4.0		0.0- 4.0		zMWU= 1.72	0.063
	Mean± SD	2.04± 1.1		1.52± 1.0			
	Median	2.0		2.0			
	P0	3	12.0%	4	16.0%	X <sup>2</sup> = 7.19	0.126
	P1	3	12.0%	9	36.0%		
	P2	11	44.0%	10	40.0%		
	P3	6	24.0%	2	8.0%		
P4	2	8.0%	0	0.0%			

$p \leq 0.05$  is considered statistically significant,  $p \leq 0.01$  is considered high statistically significant, SD= standard deviation, MWU= Mann-Whitney U Test, comparison between groups done by Student T Test & Pearson Chi-Square test

**Table (2)** shows comparison between the two groups regarding clinical characteristics.

		Group A (Laparoscopy group) (n = 25)		Group B (Methotrexate group) (n = 25)		Test value	P-value
		n	%	N	%		
Side	LT adenexia	13	52.0%	11	44.0%	X <sup>2</sup> = 0.321	0.571
	RT adenexia	12	48.0%	14	56.0%		
Previous ectopic pregnancy	No	22	88.0%	23	92.0%	X <sup>2</sup> = 0.222	0.637
	Yes	3	12.0%	2	8.0%		
Previous spontaneous abortion	No	19	76.0%	18	72.0%	X <sup>2</sup> = 0.0	1.00
	Yes	6	24.0%	7	28.0%		
History of PID	No	13	52.0%	19	76.0%	X <sup>2</sup> = 3.125	0.077

	Group A (Laparoscopy group) (n = 25)		Group B (Methotrexate group) (n = 25)		Test value	P-value
	n	%	N	%		
Yes	12	48.0%	6	24.0%		

$p \leq 0.05$  is considered statistically significant,  $p \leq 0.01$  is considered high statistically significant, Comparison between groups done by Pearson Chi-Square test

**Table (3):** Comparison between the two groups as regards greatest diameter of adenexial mass measured by trans-vaginal ultrasound.

		Group A (Laparoscopy group) (n = 25)	Group B (Methotrexate group) (n = 25)	Test value	P-value
Greatest diameter	Range	1.50- 4.80	1.20- 4.80	T= 1.42	0.162
	Mean± SD	3.29± 0.83	2.88± 1.19		
	Median	3.20	2.80		

$p \leq 0.05$  is considered statistically significant,  $p \leq 0.01$  is considered high statistically significant,

SD= standard deviation, -comparison between groups done by Student T Test

There was no statistical significant difference between the two groups ( $p=0.162$ ).

**Table (4):** show comparison between the two groups as regards Q- B HCG measurements.

	Group A (Laparoscopy group) (n = 25)		Group B (Methotrexate group) (n = 25)		Test value	P-value
Pre Q-BHCG	Range	250.0- 4565.0	740.0- 3520.0	$Z_{MWU}= 1.77$	0.077	
	Mean± SD	2362.08± 1458.76	2646.25± 1288.8			
	Median	2500.0	3162.5			
Post Q-BHCG	Range	20.0- 2300.0	193.0- 4565.0	$Z_{MWU}= 2.10$	0.037	
	Mean± SD	981.73± 684.03	1586.48± 1401.05			
	Median	950.0	1090.0			

	Group A (Laparoscopy group) (n = 25)		Group B (Methotrexate group) (n = 25)	Test value	P-value
p-value (pre/post)		0.006	0.018		

$p \leq 0.05$  is considered statistically significant,  $p \leq 0.01$  is considered high statistically significant, SD= standard deviation, - Mann-Whitney U Test and Friedman's Two-Way ANOVA

\* **Pre Q-BHCG** (Quantitative Beta human chorionic gonadotrophin) was done before intervention.

\***Post Q-BHCG** was done 1 week after laparoscopic conservative surgery while Post Q-BHCG in methotrexate group was done after demonstration of methotrexate to the value that we decide no additional injection will be given.

- ◆ There were no significant differences between the two study groups as regards pre-therapeutic  $\beta$ - HCG ( $p=0.077$ ).Also, laparoscopy group showed statistically significant decrease in 1 week post-therapeutic  $\beta$ - HCG compared to Methotrexate group ( $p=0.037$ ).
- ◆ Post-therapeutic  $\beta$ - HCG was significantly decreased in both groups compared to pre-therapeutic  $\beta$ - HCG ( $p=0.018, 006$ )

**Table (5):** show distribution of laparoscopic management among the studied women in laparoscopy group and tubal integrity.

Parameters		Laparoscopy group (n=25)	
		n	%
Laparoscopic management	Salpingostomy	13	52%
	Salpingectomy	10	40%
	Ovariectomy	1	4%
	Tubal aspiration	1	4%
Tubal integrity	No	10	40%
	Yes	15	60%

**Discussion:** During recent decades, the diagnosis and efficacy of treatment of ectopic pregnancy (EP) has progressed significantly .Surgical intervention has long been the gold standard for treatment of EP, although the medical management of un-ruptured EP is a safe and effective alternative.<sup>(12)</sup> In our study; we noticed that, the 6 women

who required more than one dose of methotrexate had a significantly higher initial serum B HCG concentration than those women who were treated successfully with only one dose. Also, it took about 4 weeks to become less than 5 IU/L in MTX group, while it took about 2 weeks to become undetectable (less than 5 IU/L) in laparoscopy group.

Success of treatment in laparoscopy group (23 cases, 92%) was more than in methotrexate group (18 cases, 72%), but no statistically significant difference between two groups ( $p=0.306$ ). Two (8%) cases in laparoscopy group who had conservative surgery (one tubal aspiration and one salpingostomy) were presented with elevated quantitative B-HCG one week after surgery due to persistent trophoblast and treated with course of methotrexate injection. While in methotrexate group; 7 cases had failed medical therapy and underwent laparoscopy.

Fertility outcome data were obtained by phone call follow-up; Rate of spontaneous pregnancy among cases in laparoscopy group: was (5 cases, 20%), while pregnancy not allowed in methotrexate group for at least 3 months due to its teratogenicity. One case (4%) had recurrent ectopic pregnancy in laparoscopy group, while no cases in methotrexate group. We noticed that women received methotrexate had heavier and more prolonged vaginal bleeding than those treated by laparoscopic surgery.

- ◆ **In agreement** with our study; **Hajenius PJ et al, 1997**, had a randomized trial on 100 patients; 49 cases included in laparoscopic group; 92% underwent salpingostomy and 8% salpingectomy, using dose 1 mg/kg IM in MTX group, one course include 4 doses, success rate was not significant; 80% in laparoscopic group versus 86% in MTX group (82% were successfully treated with only one course; 4% needed a second course). While **in contrast** with us in the same study; higher rate of persistent trophoblast (20%) in laparoscopy group was found, which may be due to higher rate of salpingostomy (92%) done in their study. <sup>(13)</sup>



- ◆ **In agreement** with our study; **Saraj et al, 1998**, had a randomized trial included 75 women, had compared single dose systemic methotrexate with conservative laparoscopic surgery; using a dose of 1 mg/kg IM. They found that difference in success rate was not significant. Success rate was 78% for single dose methotrexate compared with 92% for laparoscopic surgery. <sup>(14)</sup>
- ◆ **In agreement** with our study; **Fernandez H et al, 1998**, did other randomized trial on 100 women (49 cases included in laparoscopic group; all underwent salpingostomy), using dose 1 mg/m<sup>2</sup> in MTX group; 22 cases were injected IM and 29 cases received local injection into ectopic pregnancy mass trans-vaginally under US guidance without anesthesia. Success rate was not significant; 95.9% for laparoscopy group (47 of 49) versus 88.2% for single dose methotrexate and 4% had persistent trophoblast in salpingostomy group. <sup>(15)</sup>
- ◆ **In agreement** with our study; **Krag Moeller LB et al, 2009**, did another randomized study included 106 women (53 for each group) using dose 1 mg/m<sup>2</sup> of systemic MTX injection, in laparoscopy group; tube was preserved in 32 cases (60%) who had salpingotomy, while 21 cases (40%) had salpingectomy. Success rate of laparoscopic surgery was 87% and not significantly different from that in the MTX group which was 74%. While **in contrast** with our study in the same study; **they** found higher rate of spontaneous intrauterine pregnancy; 73% after MTX therapy and 62% after laparoscopic surgery and also higher rate of recurrent ectopic pregnancy (17.3% after laparoscopy and 9.6% after MTX therapy), this often due to higher number of studied cases (106) and longer duration of follow up (about 3 years). <sup>(16)</sup>
- ◆ **In agreement** with our study; **Sowter MC et al, 2001**, had a prospective randomized trial on 62 cases whose serum B-HCG less than 5000 IU/L, and adnexial mass diameter was less than 3.5 cm, 28 cases included in laparoscopic group; 64% underwent salpingostomy and in 8% tubal aspiration, 28% salpingectomy. Using dose 50 mg/m<sup>2</sup> IM in MTX group (34 cases), success

rate was not significant ; 93% in laparoscopic group compared to 85% in methotrexate group (65% treated successfully with single dose and 26% needed more than one dose but only 20% of them had successful medical therapy) .Also rate of persistent trophoplast in laparoscopy group was 7% .<sup>(17)</sup>

- ◆ **In contrast** of our study; **Lewis-Bliehall C, et al, 2001** had a comparative study on 401 cases, **30%** treated with MTX, **69%** surgical management (**63%** laparoscopy and 37% laparotomy). They found that success rate of methotrexate therapy was significantly lower than that of laparoscopic surgery (79% versus 90%) ; P = 0.02, this is often due to lower number of cases in MTX group (only 119, 30%) versus 172 women (63%) who underwent laparoscopy in this study.<sup>(18)</sup>
- ◆ **In agreement** with our study; **Jurkovic D et al, 2017**, did a placebo-controlled randomized trial on 80 cases with tubal ectopic pregnancies and their Q-B HCG was less than 1500 IU/L; 42 women included in MTX group received 50 mg /m2 of systemic MTX injection .they found success rate of MTX was 83% which is little higher than success rate of MTX therapy in our study (72%), this is often due to lower level of initial B-HCG (less than 1500 IU/L) in their study.<sup>(19)</sup>
- ◆ **In contrast** of our study; **Lavie G et al, 2021**, had a retrospective observational study on 119 cases with serum B HCG level less than 5000 IU/L, the overall age was  $30 \pm 5.5$  years (range 20–47) and absence of foetal heartbeats in US. They found lower rate of success of single dose MTX (65%) which may be due to success of MTX therapy in their study was depended on decrease in  $\beta$ -HCG between day 4 and day 7 to level less than 15% with no need for second injection of MTX or surgical intervention.<sup>(20)</sup>

**Conclusions:** Laparoscopic surgery is as effective as methotrexate therapy for conservative management of undisturbed adenexial ectopic pregnancy and methotrexate has advantage of being non-invasive procedure. Also postoperative

serum B-HCG monitoring is necessary for early detection of persistent trophoblast after conservative surgery. .

### **Ethical Approval and Consent:**

An informed written consent was obtained from all studied cases. The study was done after ethical approval from the Institute Ethics Committee of faculty of medicine.

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