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ORIGINAL ARTICLE

Outcome of Methotrexate Therapy in The Management of Undisturbed Tubal Ectopic Pregnancy

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ABSTRACT

Background: Ectopic pregnancy (EP) is implantation of the fertilized egg outside endometrial cavity of uterus. Diagnosis of anectopic pregnancy is vital , as it can save mother's life before tubal rupture takes place . Tubal rupture accountsfor 6% of deaths related to pregnancy . Ectopic pregnancy is treated either by expectant management , methotrexate or surgical treatment. **Objectives**: in this study we assess the association between using of Methotrexate and cure of undisturbed tubal ectopic pregnancy .**Methods**:a clinical trial was performed on 16 patients with undisturbed tubal ectopic pregnancy . **Patients** are given I.M methotrexate by a dose of 1 mg/kg or Body Surface Area (BSA) dose based of 50mg/m2 and follow up of the outcome either cure , laparoscopy or laparotomy.**Results**: There are statistically non-significant differences between responder and non-responder regarding age , BMI, gravidity, mass position, parity, history of abortion, gestational age and mode of delivery .Alsowe found that by the end of the first week after methotrexate intake, the decline in β-hCG was statistically significant among responders (p value =0.001) while non-responders show non-significant change(p value = 0.120).we alsofound that 11patients respond to methotrexate therapy (68.7%) while the remaining 5 patients were non responders .**Conclusion**: We concluded that Methotrexate is an effective medical management for an ectopic pregnancy especially when conservation of fallopian tube is needed .

Key words: undisturbed, tubal, ectopic, pregnancy, methotrexate.

INTRODUCTION

Ectopic pregnancy (EP) is implantation of the fertilized egg outside endometrial cavity of uterus. In women presenting to emergency department complaining of symptoms of abdominal and or pelvic pain or vaginal bleeding, and they are pregnant, an ectopic pregnancyshould be considered [1].

It is acute emergency if not immediately diagnosed and treated. Immediate diagnosis and appropriate management can reduce the risk of maternal morbidity and mortality which is related to an ectopic pregnancy. It isvery important to exclude it when women present with bleeding in an early pregnancy [2].

Systemic methotrexate (MTX) is commonly usedasa conservative first-lineof treatment for patients having ectopic pregnancy. Data provided bythe randomized controlled trials indicates that systemic Methotrexate should be only used in selected patients having EP. Important criteria for selection are the size of EP, absence of the fetal cardiac pulsation on TVS, as well as maximum concentrations of human chorionic gonadotrophin (β-hCG) [2].

Aim of work

To assess the association between using of Methotrexate and cure of undisturbed tubal ectopic pregnancy.

PATIENTS

This clinical trial was carried out on sixteen women diagnosed as undisturbed ectopic pregnancies. IRB approval was obtained before starting the study .The cases were collected over 6 months. Written informed consent was obtained from all participants, the study was approved by the research ethical committee of Faculty of Medicine, Zagazig University. The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.the patient age ranged from 21 to 38 years and their BMI ranged from 23 to 40 (as shown in table 1)

METHODS

Patients are given methotrexate dose of 1 mg/kg or Body Surface Area (BSA) dose based of

50mg/m2 (BSA is calculated according to the following equation), I.M. and follow up of the outcome either cure , laparoscopy or laparotomy.

Body Surface Area (BSA) (Mosteller Method) =

$$\sqrt{\frac{Height\ (cm) * Weight\ (Kg)}{3600}}$$

Patients were advised to avoid vitamin containing folic acid, non-steroidal anti-inflammatory drugs and sexual intercourse while taking MTX.

Before methotrexate injection , patient should be counseled on the risks, benefits, side effects, and possibility of the failure of this medical therapy, which can result in a tubal rupture and need surgery. Patients must be aware of signs and symptoms of tubal rupture and advised to contact with their physician when significant worsening of abdominal pain / tenderness, a heavy vaginal bleeding , tachycardia ,dizziness, palpitations, or syncope.

Patient inclusion Criteria are 1-Patients with beta human chorionic gonadotrophin (β-hCG) levels of ≤ 5000 mIU/ml 2- Patients who are hemodynamically stable. 3-Absent cardiac activity. 4- Adnexal mass ≤ 4 cm. 5- Presence of hemoperitoneum< 100 ml. 5- Normal blood count , liver and kidney functions.

Patient exclusion Criteria are: 1- Hemodynamically unstable. 2- Patients with beta human chronic gonadotrophin. 3- (β-hCG) levels of > 5000 mIU/ml. 4- Hypersensitivity to methotrexate . 5- Presence of fetal cardiac activity. 6- Adnexal mass > 4 cm

Follow up:

β-hCG was followed on day one (injection day), day four, on day seven.

If decrease in β-hCG between days 4 and day 7 is15% or more , this is successful treatment..

Weekly measurements are continued until the β-hCG is undetectable.

If decrease in β-hCG between days 4 and day 7 is less than 15%, a second dose of methotrexate 50 mg/m2 was give (maximum 3 doses).

STATISTICAL ANALYSIS

Data were entered checked and analyzed using Epi-Info version 6 and SPP for Windows version 8 [**11**].

Data were summarized using:

The arithmetic mean:

As an average describing the central tendency of observations

The Standard Deviation (SD):

Asa measure of dispersion of the results around the mean

Correlation study:

Correlation between variables was done using correlation coefficient "r". This test detects if the change in one variable was accompanied by a corresponding change in the other variable or not.

Student t test:

This is the test used in the statistics of this study. It was used when comparing two means.

Level significance:

For all above mentioned statistical tests done, the threshold of significance is fixed at 5% level (p-value).

The results were considered:

- Significant when the probability of error is less than 5% ($p < 0.05$).
- Non-significant when the probability of error is more than 5% ($p > 0.05$).
- Highly significant when the probability of error is less than 0.1% ($p < 0.001$).

The smaller the p-value obtained, the more significant are the results.

RESULTS

There are statistically non-significant differences between responder and non-responder regarding age , BMI, gravidity, mass position, parity, history of abortion, gestational age and mode of delivery(as shown in figure 1 and table 2). Also we found that by the end of the first week after methotrexate intake, the decline in β-hCG was statistically significant among responders (p value = 0.001) while non-responders show non-significant change (p value = 0.120)(as showon in figure 3 and table 4). we also found that 11 patients respond to methotrexate therapy (68.7%) while the remaining 5 patients were non responders,out of them 2 cases were heamodynamically unstableand needed laparotomy ,the remaining 3 cases needed laparoscopy .(as shown in figure 2 and table 3)

Table 1: Demographic and clinical criteria of studied cases

	Mean ± SD	Range
Age	28.19 ± 5.18	21 – 38
BMI	28.86 ± 4.21	23 – 40

Table 2: obstetric history of studied cases

	Mean ± SD	Median	Range
Gestational age	**6.56** ± 0.8	**7**	**4 – 8**
Gravidity	2.88 ± 1.31	3	1 – 6
Parity	1.63 ± 1.2	2	0 – 4
Abortion	0.25 ± 0.45	0	0 – 1
	N	**%**	
Mode of delivery No Vaginal delivery CS	 3 6 7	 18.8 37.5 43.8	

Table 3: fate of studied cases after methotrexate treatment:

	N (16)	%
Fate: Resolution Disturbed ectopic • One day • Two days Increased adnexal mass Tubal hematoma	 11 1 1 1 2	 68.7 6.3 6.3 6.3 12.4
	N (5)	
Decision in non-responder: Laparoscopic salpingectomy Laparotomy	 **3** **2**	 **60** **40**

Table 4: change in β- HCG in responder and non-responders over time:

	Responder		Non-responder		MW	P
	Mean ± SD	**Median**	**Mean ± SD**	**Median**		
Day1	2139.73±**1243.22**	1998	**2907±020.13**	2411	-1.303	0.193
Day 4	1252.7±774.54	987	2876±776.19	3100	-2.102	0.036
Day 7	541.13± 253,37	450	2277.5±**1728.88**	2277.5	-2.171	0.03
First week	240.81 ± 162.63	200	2182.5±**1721.81**	2182.5	-2.174	0.03
P (Frideman)	<0.001**		0.120			
Second week	95.98 ± **123.91**	30				
Third week	32.39 ± **60.87**	0.55				
Fourth week	11.68 ± **20.99**	1.8				
P (Frideman)	0.001**					
Fifth week	0.1	1				

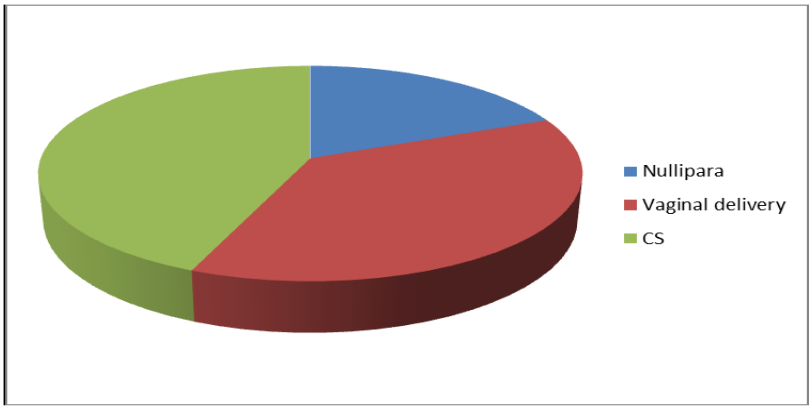

Figure 1: Pie chart showing mode of delivery in studied cases

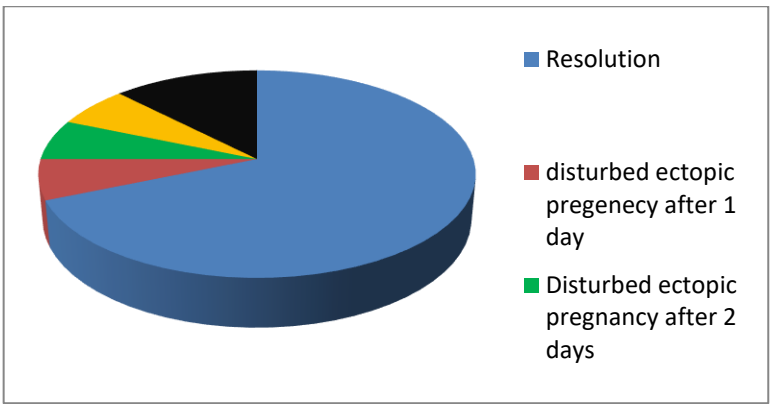

Figure 2: Pie chart showing fate of ectopic pregnancy among studied patients**.**

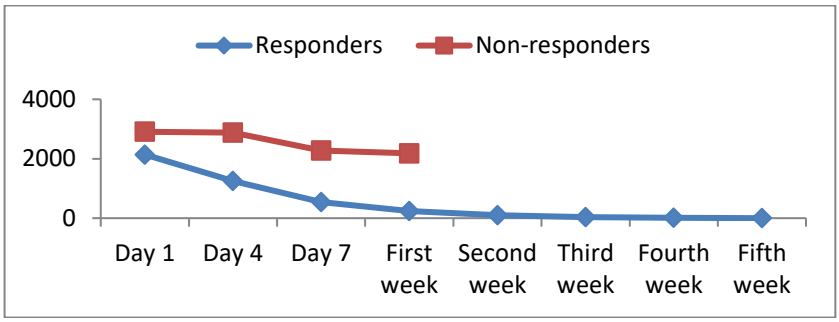

Figure 3: Multiple line graph showing change in β- B-HCG in responder and non-responders.

DISCUSSION

ectopic pregnancy, is pregnancy that implants outside uterine cavity. It is dangerous for the mother, as internal bleeding iscommon complication.Tubal ectopic pregnancy occurs due to combination ofthe retention of embryo in fallopian tube due to impaired embryo-tubal transport and also alterations of tubal environment allowing early implantation to happen[3].

Hopkisson [4] reported that incidence of an ectopic pregnancy is rising & still account for a very significant number of deaths observed in the last confidential enquiry of the maternal deaths.The ectopic pregnancy accounted for 11 deaths out of 15 cases in early pregnancy in the 2000-2002 report. Six of these 11 deaths were associated with the substandard care

In this study , we discuss effectiveness of methotrexate in the treatment of undisturbed tubal ectopic pregnancy . Our study includes 16 patients with undisturbed tubal ectopic pregnancy ,all were given methotrexateintramuscular injection. The age group of these patients ranged from 21 to 38 years old & Its mean was 28.19 ± 5.18.

The obstetric history of these studied cases showed that Seven patients (43%) had parity < 2 and nine patients (57%) had parity ≥ 2. The gestational age at diagnosis in the studied cases was ranged from 4 to 8, its mean was 6.56 ±0.8 .

All patients were given methotrexate by intramuscular injection. With a dose ranging from 50-100 mg . its mean was71.88 ± 20.16.this study includes patients that have adnexal mass size is less than or equal to 4cm .its mean was 2.89 ± 0.68 &serum β-hCG of these patients is less than 5000 mIU/ml . its mean was 2139.73±1243.22 among responders and 2907±020.13 among non responders&and amount of heamoperitonium is minimal .This is in agreement with **Dhar et al . [5]**which is retrospective study was carried on 60 patients with diagnosed as ectopic pregnancy and treated in-patients with a single-dose methotrexate regimen .

The overall success rate oftreatment by methotrexate in our study was 68.7% (n= 11). Surgical intervention was requiredfor 31.3% (n=5) of patients .Out of these patient who need surgical intervention , 12.6% (n=2) patients developed tubal rupture and increased heamoperitonium that need urgent laparotomy with salpingectomy . While 18.7 % (n=3) developed tubal heamatoma and increased adnexal mass that required earlysurgical intervention by laparoscopy and salpingectomy .

Juneja et al.[6] reported success rate of 93% .**Also Srivichai et al.[7]** reported a success rate of 90.6% in which 96 out of 106 patients were successfully treated with methotrexte.While **Dhar et al.[5]** reported a success rate of 65%.this correlate with success rate in our study.

In most of comparative studies, success rate was higher than in our study. The reason is that at beginning of methotrexate regimen in our hospital women with increasing β-hCG values and complaint of abdominal pain were taken early for the surgical intervention for fear of tubal rupture .

Mahboob et al. [8] reported the success rate of 80% by treating 12 out of 15 women with a single dose MTX with an initial β-hCG levels of 5000 mIU/ml .

Mamdoh [9] demonstrated that the β-hCG of 2000 mIU/ml is optimum cutoff value to select potential cases for medical failure in using the single dose approach as cases with initial β-hCG value of > 2000 mIU/ml and/or in embryonic sac size of > 3.4 cm should be carefully monitored for the treatment failure. This correlates with our study asthe failure rate was highest with adnexal mass of ≥ 4 cm. In the same series, increase in treatment failure group with advanced maternal age ≥ 35 years and the history of spontaneous abortions was noted which is not corresponding to our study where success rate of MTX was not affected by maternal age as in our study ,There are statistically non-significant differences between responder and non-responder regarding age.

Thai et al.[10] noted the time of ectopic pregnancy resolution was 33 days with single dose, similar to our study.

CONCLUSION

We concluded that Methotrexate is effective medical management forthe ectopic pregnancies in society where conservation of tubes is important.

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