INTRAVENOUS METHOTREXATE FOR THE TREATMENT OF UN-RUPTURED ECTOPIC PREGNANCY

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ABSTRACT

Objectives: To evaluate the efficiency and safety of intravenous methotrexate as an alternative to surgery for the treatment of un-ruptured tubal pregnancy as well as cost effectiveness.

Design: A cohort study.

Setting: Madina Maternity and Children's Hospital (MMCH). Al Madinah Al Munawarah. KSA. Period from 9/02/2005 to 26/06/2006 (01/01/1426H to 30/05/1427H)

Methods: The authors studied thirty four patients with un-ruptured tubal ectopic pregnancies, clinically stable, who were treated with intravenous methotrexate according to a single-dose protocol. Pretreatment serum concentrations of human chorionic gonadotrophin (hCG) and progesterone, endovaginal ultrasonography to asses size of the mass, fetal cardiac activity and the presence of fluid in the peritoneal cavity (presumably blood) were done. All were correlated with the efficiency of therapy as defined by resolution of ectopic pregnancy (decline in hCG level to 15 mIU/ml or less) without the need for surgical intervention. The outcome measures also included the frequency of preservation of the tubes, subsequent ipsilateral tubal patency and further pregnancy within one year.

Results: The success rate was 88.2%. Thirty four patients of forty one (34 of 41) diagnosed as ectopic pregnancy were treated with intravenous methotrexate (82.9%). Twenty eight of thirty four (82.35%) were successfully treated with a single-dose intravenous methotrexate. Six patients (17.65%) needed a second dose of methotrexate. The mean serum chorionic gonadotrophin and progesterone concentrations were 3247.53 mIU/ml ± SD 348.1 and 8.54 ± 13.1 ng/ml respectivley. The mean time needed for serum hCG concentration to reach 15 mIU/ml or less (the resolution time) was 35.1±SD 12.8 days. Subsequent pregnancy rate within one year was 69.2% (9 women of 13). Side effects to methotrexate therapy were minimal.

Conclusion: Single dose of intravenous methotrexate therapy was well tolerated, cost-saving, non surgical, fallopian tube saving treatment for un-ruptured ectopic pregnancy

INTRODUCTION

Until the 1970s, the management of ectopic pregnancy was by open exploratory surgery [1]. Nowadays, with the advances in technology, high resolution ultrasonography and sensitive serum assays for human chorionic gonadotrophin concentrations allow prompt, reliable non-invasive diagnosis of ectopic pregnancy [2,3]. As the

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sensitivity of these tests has increased, the need for laparoscopy to confirm the diagnosis has decreadsed. In fact, with current techniques, ectpoic pregnancy can be diagnosed reliably without the need for laparoscopy.

Worldwide, there has been a marked increase in the absolute number and rate of ectopic pregnancy in the last two decades with an increase of four folds. In the USA, for instance, from 1970 to 1992. The incidence is increased with increasing age [4]. The rise can be attributed partly to an increase in certain risk factors and partly to improved diagnosis. Some ectopic pregnancies detected today, for instance, would have spontaneously resolved without detection or intervention in the past.

The incidence of ectopic pregnancy in Madina Maternity and Children's Hospital (MMCH) during the years 2004, 2005 and until 26/06/2006 was 5.6 , 5.4 and 7.7 per thousand deliveries respectively whereas the overall incidence of ectopic pregnancy in Al Madinnah Al Munawarrah city including Ohud hospital and all eight private hosptials was 6.3, 5.8 and 7.3 per thousand deliveries respectivley. Table I.

In 1956, Li & colleges were the first to report the effective use of methotrexate (MTX) for the treatment of gestational trophoblastic diseases [5].

Tanaka et al[6] reported successful treatment of ectopic pregnancy with intramuscular methotrexate in 1982. Stoval and Ling [7] described the one dose protocol.

Until late 90s experiences with the single-dose protocol has been described in the literature for more than 1500 cases with success rates ranging from 71% and 100% [8-12]. Despite this, use of methotrexate remains somewhat controversial.

Women most likely to respond to methotrexate treatment are thought to be those with small masses, lower serum concentrations of hCG and progesterone and the absence of blood in the peritoneal cavity. But it has been difficult to determine the true effect of those characteristics on success rates because of the small size of previous studies [13,14,15].

OBJECTIVES

The purpose of this study was to evaluate the efficiency and safety of intravenous Methotrexate (MTX) therapy as an alternative to surgery for the treatment of unruptured ectopic pregnancy

METHODS

Subjects:

Forty one (41) patients diagnosed as ectopic pregnancy presented to Madina Maternity and Children's Hospital (MMCH), unit D division between February 2005 and June 2006. The authors conducted a prospective study of thirty four patients with ectopic pregnncies who had been treated with intravenous methotrexate by members of Unit D divison of MMCH, Al Madinah Al Mounawarrah, Saudi Arabia, to identify the safety and efficiency of therapy as well as the cost effectiveness. All women and their husbands gave written informed consents before treatment.

Diagnosis:

The diagnosis of tubal pregnancy was made by measuring serum concentrations of hCG and progesterone (16). Endovaginal ultrasonography was performed initially for all suspected women with ectopic pregnancy. Women with serum concentrations of hCG more than 10.000 mIU and serum progesterone of more than 25 ng/ml were further evaluated. All women were followed up with serial measurements of serum hCG. Endovaginal ultrasonography was performed in woemn when concentrations of hCG reached 2000 mIU/ml. Ectopic pregnancy was diagnosed in these women if an intrauterine gestational sac was not seen and the serum level of hCG continued to rise and/or an adnexal mass could be identified. Women with

concentrations of hCG of less than 2000 mIU/ml with inappropriate increase (less than 50% in 24 hrs) were subjected to diagnostic laparoscopy. Three women had dilatation and curettage (D&C) performed.

Study Protocol:

Briefly, women with ectopic pregnancies were considered candidates for methotrexate treatment (inclusion criteria) if:

- Were hemodynamically stable
- Asymptomatic or mildly symptomatic. Did not have the free peritoneal fluid outside the pelvic cavity.
- Did not desire surgical treatment.
- Agree to give two written consents: one for methotrexate therapy with the possibility for a repeated dose if needed, and the other for possible open exploratory surgery in case of failure of methotrexate therapy.
- Agree to weekly follow up until serum concentration of hCG decreased to 15 mIU/ml or less.
- No sonographic evidence of fetal heart activity.
- Did not have hepatic, hematologic or renal diseases (as evidenced by serum aminotrasferase concentration more than twice, the upper limit of WBC less than 15,000/mm, a platelet count of less than 100,000/ml or serum creatinine of more than 133 mmol/l).

Exclusion criteria:

- Women with moderate to severe abdominal pain or adnexal tenderness.
- Mass size of more than 4.2 cm

The size of the gestational mass as determined by endovaginal ultrasonography had to be 4.2 cm or less, and the initial serum human chorionic gonadotrophin concentrations of up to 10.000 mIU/ml. Patients with concentrations of more than 10.000 were further evaluated clinically.

All women received intravenous methotrexate as a body weight (BW) dependant dose. Women below 50kg. BW received 50 mg methotrexate, whereas those above 50 kg received 100 mg (mean BW was 68.19±11.99). The dose was diluted in 200 cc 0.9% saline and was infused over a period of 2 hrs.

Serum hCG concentration was measured on day 4 and day 7. If the concentration did not decline by at least 15% on day 7, a second methotrexate dose was given . If serum hCG concentration declined by at least 15%, the measurements were repeated weekly until the concentrations reached 15mIU/ml or less.

If a repeated dose of methotrexate was given, the day of administration of the second dose was considered a new Day 1. The repeated dose was given intravenously according to BW in kg (i.e. 1mg/kg/WB).

Treatment success was defined as the achievement of a serum hCG concentration of 15mIU/ml or less without the need for surgical intervention.

Women with serum hCG concentrations of less than 3000 mIU/ml were discharged home 4 hrs after treatment with methotrexate, while those with concentrations above 3000 mIU/ml were kept in the hospital until evidence of success i.e. decline in hCG concentrations by at least 15%.

Serum hCG concentrations and progesterone were measured by Electrochemiluminescence immunoassay (ECLIA) using Elecsys 2010 laboratory machine.

The size of the gestational mass was defined as its maximal diameter in any dimension as measured by endovaginal ultrasonography. Ultrasonography was repeated on day 4 and day 7.

Hysterosalpingography (HSG) was performed 3 months after the end of successful treatment.

RESULTS

There were 41 women with ectopic pregnancies diagnosed in MMCH during the period between

February 2005 and June 2006.

38 women were Saudi (92.7%) while the rest were non Saudi (7.3%).

Table II illustrates the mode of treatment of 41 women presenting with ectopic pregnancy.

Thirty four patients (82.93%) were treated by a single-dose intravenous methotrexate for unruptured ectopic pregnancy. Seven had exploratory laparotomy and Salpingectomy was performed. These seven patients did not meet the criteria for methotrexate therapy as there were three patients with ruptured ectopic pregnancy, whereas the other four patients had gestational masses of more than five cm. Table II.

Two patients had a previous history of ectopic pregnancy, one of them was previously treated with methotrexate. This was followed by another recurrent ectopic pregnancy (third ectopic pregnancy in the same patient). Although she met the inclusion criteria, the preferable treatment was open exploratory laparotomy to prevent further occurrence of further ectopic pregnancies.

The accuracy of ultrasonographic examination regarding site and mass size was 100%; the characteristics of the total number of women treated with single- dose protocol methotrexate (N=34) are shown in Table IV.

Among the 34 women treated with methotrexate, ultrasonography revealed an ectopic mass in 28 women (82.35) with one mass of 4.2 cm containing a fetal echo without fetal cardiac activity. The mean diameter of the masses was 2.1±0.28 cm (from 1.0 to 4.2 cm). The average period of amenorrhea in the treated group was 44.35 ± 10.078 days (range from 33 to 64 days).

Fourteen patients (41.2%) had ultrasonographic evidence of free peritoneal fluid confined to the pelvis. They were labelled as mild free peritoneal fluid.

The overall success rate of treatment with methotrexate was 88.24%. Twenty eigh patients (82.35%) received one dose intravenous methotrexate whereas in six patients (17.65%) a second methotrexate dose was needed on day7.

Four patients had to have open exploratory laparatomy. Salpingectomy was performed due to mismanagement . They were considered as treatment failures because surgery was performed.

Three patients had diagnostic laparoscopy, two of them prior to methotrexate therapy and one patient had the laparoscope on Day 4 due to hemoperitoneum (moderate blood collection) following separation pain. In three patients, diagnostic D&C was performed prior to treatment. Histopathology revealed no chorionic villi

History and presenting signs and symptoms seen among women with ectopic pregnancy treated with MTX are shown in Table V.

Post treatment follow up:

Only seventeen patients of those treated medically could be traced for tubal patency with HSG, all had patent fallopian tubes.

The mean initial serum hCG concentration was 3247.53±3408.1 mIU/ml (from 993 to 17780 mIU/ml).

The mean time required for the serum hCG concentration to fall to 15 mIU/ml or less (the resolution time) was 35.1±12.8 days. (From 19 days to 84 days).

Nine patients had several bouts of mild to moderate abdominal pain at the site of the ectopic pregnancy between day 4 and day 9. Mild to moderate hemoperitoneum was diagnosed in 8 of them. In four of these women an open exploratory laparotomy (at night time) was performed . All were hemodynamically stable. At laparotomy all were found to have intact fallopian tubes with mild to moderate hemoperitoneum (50-200 cc of blood) confined to the pelvis. They were diagnosed as

separation pain with tubal abortion. These 4 patients had an initial serum hCG concentration of 4148.3 ± 3867.96 mIU/ml (993, 1857, 9596 and 4147) and serum progesterone concentration of 5.95 ± 5.12 ng/ml. Mass size was also not different from other women 2.28 ± 1.47 cm. They had the serum hCG concentration elevated on day 4 (Table VI).

Six patients (17.65%) required a second methotrexate dose on day 7. The mean initial serum hCG concentration of these six women was 4582.2 ± 2822.8 mIU/ml on D1 and 5729.7 ± 3240.0 mIU/ml on D7 and a serum progesterone level of 13.827 ± 22.8 ng/ml (7.6, 60, 0.33, 3.2, 7.6 and 4.2). The mass size was not different from other treated patients 2.47 ± 0.92. In these patients, the resolution time of hCG levels was relatively longer (47.8 ± 11.1 days) Table VII.

No patients required more than 2 doses.

Table VIII shows a comparison between patients who received one methotrexate dose and those receiving two doses.

In sixteen patients (47.1%), the serum hCG concentration were elevated on day 4. In ten of them, the concentrations declined by more than 15% on day 7. Side effects to methotrexate treatment were minimal. They were observed in one patient in the form of mild self-limiting diarrhea lasting for 16 hrs. All patients were monitored by endovaginal ultrasonography on days 4 and 7; the mass size was unchanged. These results were irrespective of the serum hcG concentrations.

Nine women of thirteen (69.2%) conceived after one year treatment. This resulted in seven term deliveries and one spontaneous abortion, whereas one patient had another ectopic pregnancy on the same previously treated tube with methotrexate for an ectopic pregnancy. This represents 11.1%.

11 patients had Chlamydia titer done, one was positive for IgG antibodies.

DISCUSSION

We faced some difficulties explaining to the women the nature of methotrexate treatment as a safe single dose chemotherapeutic agent and convincing them to accept the protocol. Thus all treated women had to be admitted to the hospital (Gynecology department) rather than being treated on an outpatient basis.

The results of this study support the use of intravenous methotrexate for the treatment of un-ruptured ectopic pregnancy. A comparison between intravenous and intramuscular routes of methotrexate (Table IX) shows that there is no statistical differences regarding age, parity and abortions.

In the current study, the mean initial serum chorionic gonadotrophin concentration was higher than that reported by Khaled B (Al Qassim), Stika et al and Glock et al. Meanwhile the overall success rate (88.2%) is almost equal to that of Khaled B (86.7%), Glock et al (85.7%) compared to Stika et al (78%), Stoval & Ling (94.2%). The incidence of women requiring second dose of methotrexate in this current study was 17.6% which was hgiher than that reported by Stoval & Ling (3%), and Glock et al (5.9%) but was lower than that reported by Stika et al (22%), and Khaled B (20%). In this study, as well as that of Stoval & Ling and Glock et al, no patients required more than two doses[7, 16-18].

In this current study as well as that of Stoval & Ling[7], the resolution time (35.1 ± 12.8 and 35.5 ± 12 days) was longer than that of other reports. This was due to the higher initial serum HCG concentrations in both studies (3247.53 ± 3408.1 nad 3950.6 ± 1193 mIU/ml) compared to that of Khaled B (2209 ± 1381 mIU/ml), Stika et al (1896 ± 2399 mIU/ml) and Glock et al (1388.1 ± 464 mIU/ml)[14,16,18].

The higher the serum concentrations of human chorionic gonadotrophin, the longer the resolution time. In this study, patients with serum HCG concentrations above 4000 mIU/ml had a resolution

time of 53.6 ± 18.1 days whereas those with serum concentrations below 4000 mIU/ml had a resolution time of 30.84 ± 11.14 days.

Because of the limited evidences, most of the previously published protocols for systemic methotrexate treatment of women with ectopic pregnancies have restricted treatment to women with gestational mass of less than 3 cm in size. Many other protocols further restrict treatment :o those with initial serum hCG concentration usually bellow 5000 mIU/ml. The presence of fetal cardiac activity or free peritoneal fluid is often considered as a contraindication to methotrexate treatment.

- In a review of 23 studies (all from 1990 and earlier):
- 3% failure rate for hCG concentrations below 5000 mIU/ml.
- 37% failure rate for concentrations above 10,000 mIU/ml.

The authors concluded that serum hCG concentrations abov 10,000 mIU/ml was a risk factor for failure [4].

Stika et al treated 50 patients with methotrexate. They concluded that those women with initial serum hCG concentrations above 5000 mIU/ml had a greater probability of requiring either surgical intervention or multiple doses of methotrexate[18]. Of interest was that non of the 11 patients in whom treatment was unsuccessful had an initial serum hCG concentration above 3490 mIU/ml. This could be due to their inclusion criteria.

The size of the ectopic gestation mass is frequently used as exclusion criteria for methotrexate therapy. Few data are available. In 10 women treated, the success rate was 90% in those masses between 3.0 and 3.2 compared with 93% for masses of less than 3.0 cm [11].

The presence of fetal cardiac activity has also been considered as a contraindication for methotrexate therapy although success rates have been reported when fetal heart activity was present in 88% [11].

The presence of free peritoneal fluid is considered to many as a contraindication, because it may indicate an ongoing tubal rupture. Historically, 70 to 83% of women with ectopic pregnancies had blood in the peritoneal cavity, as detected by culdocentesis, but only 50-62% of them had ruptured fallopian tubes [19].

Thus many women with ectopic pregnancy who do not have ruptured tubes have free peritoneal blood. In this study, 41.2% of the treated group had ultrasonographic evidence of free peritoneal fluid. the presence of this free fluid did not affect the success rate in this study.

In this study the presence of fetal cardiac activity was a contraindication to methotrexate treatment for some medico legal and social aspects, The size of the mass was not more than 4.0 cm. The presence of free peritoneal fluid was not a contraindication to treatment.

Patients treated for ectopic pregnancy with systemic methotrexate frequently have increased lower abdominal pain within several days of treatment[7]. This pain is often referred to as separation pain because it is commonly believed to result from tubal abortion or hematoma formation with distension of the fallopian tube. At many centers, including this institute (MMCH), patients with anything more than mild pain, with mild rebound tenderness or free fluid in pouch of Douglas undergo surgery. It has been the authors' experience that many of these women can be safely managed conservatively without surgery even in the presence of rebound tenderness or free peritoneal blood.

From our observations, it's the mass size (in particular a gestational sac of more than 5 cm) when associated with abdominal pain is the main factor for failure of medical treatment irrespective of the serum hCG concentration. Whereas smaller gestational masses (less than 4.2 cm) even with high serum hCG concentrations, are associated with high success rates.

All the factors found to affect the success rate of treatment are related to overall health of the conceptus. Large adnexal masses with high levels of serum hCG and progesterone ae associated with an

ectopic conceptus that is still developing and growing. The presence of fetal cardiac activity indicates enough vascular support for the pregnancy to continue. This explains the failure rates in such patients as well as th multiple dose treatment with methotrexate. Conversely, low concentrations of hCG and progesterone or the absence of fetal cardiac activity may indicate a very early or failing ectopic pregnancy, thus methotrexate is more effective in such women.

Table I : Prevalence of ectopic pregnancy per thousand deliveries in Al Madinnah Al Munawarrah city years 2004, 2005 and until 30/06/2006.

		MMCH	Ohud	Private
2004	No. of ectopics	78	23	48
	Total No. of pregnancies	13963	2513	7096
2005	Percentage	5.6	9.1	6.7
	No of ectopics	73	12	52
2006	Total No. of pregnancies	1363	2426	7680
(1/01 - 30/06)	Percentage	5.4	4.95	6.8
	No. of ectopics	41	9	22
	Total No. of pregnancies	5311	1010	3545
	Percentage	7.7	8.9	6.2

Table II : Mode of treatment of women with ectopic pregnncy (N = 41).

	No.	%
1- Surgical intervention	7	17.1
a) ruptured ectopic	3	7.3
b) mass > 4.2 cm	4	9.8
2- Medical treatment	34	82.9
a) one dose MTX	28	68.3
b) two doses MTX	6	14.6
Total	41	100

Table III : Comparison between women treated medically and those treated surgically for ectopic pregnancy.

Age (years)	27.9 ± 5.97	30.1 ± 5.7	0.7
Parity	2.03 ± 2.29	2.3 ± 1.7	0.38
Abortions	0.88 ± 1.26	0.86 ± 1.6	0.16
Weight (kg)	68.2 ± 1199	70.6 ± 12.9	
Gestational age (days)	44.35 ± 10.78	57.1 ± 23.4	0.25
Mass size (cm)	2.1 ± 0.82	4.9 ± 2.3	0.05
Free peritoneal fluid	14 (41.2 %)	5 (71.4 %)	
HCG mIU/ml	3247.5 ± 3408.1	4857 ± 5443.5	0.34
Progesterone level (ng/ml)	8.54 ± 13.1	17.4 ± 32.78	
Resolution time (days)	35.1 ± 12.8	0	
Subsequent pregnancy	9/13	Not followed	

Table IV : Characteristics of the treated group (n = 34).

Success rate	30/34	88.24
Number of doses :		
- One dose MTX	28/34	82.35
- Two doses MTX	6/34	17.65
Adnexal masses on USS	28/34	82.35
Free peritoneal fluid	14/34	41.2
15% fall of hCG on D4	16/34	47.1
Subsequent pregnancy :	9/13	69.2
- intra uterine	8/9	88.9
- extra uterine	1/9	11.1
Character	N	SD
Age (years)	27.9	9.7
Parity	2.03	2.29
Abortions	0.88	1.26
Weight (Kgs)	68.19	11.99
Gestational age (days)	44.35	10.78
Mass size (cms)	2.1	0.28
Mean β hCG (mIU/ml)	3247.53	3408.1
Progesterone (ng/ml)	8.45	13.1
Resolution time (days)	35.1	12.8

Table V : Clinical data of the studied group (n = 34).

Vaginal bleeding	11	32.4
Abdominal pain	6	17.7
Vaginal bleeding and abdominal pain	13	38.2
No symptoms	4	11.8
Adnexal tenderness	3	8.8
Abdominal tenderness	3	8.8
Previous H/O infertility	8	23.5
Previous H/O IUCD use	6	17.7
Previous H/O ectopic pregnancy	2	5.9
Previous H/O pelvic surgery	8	23.5

H/O History of

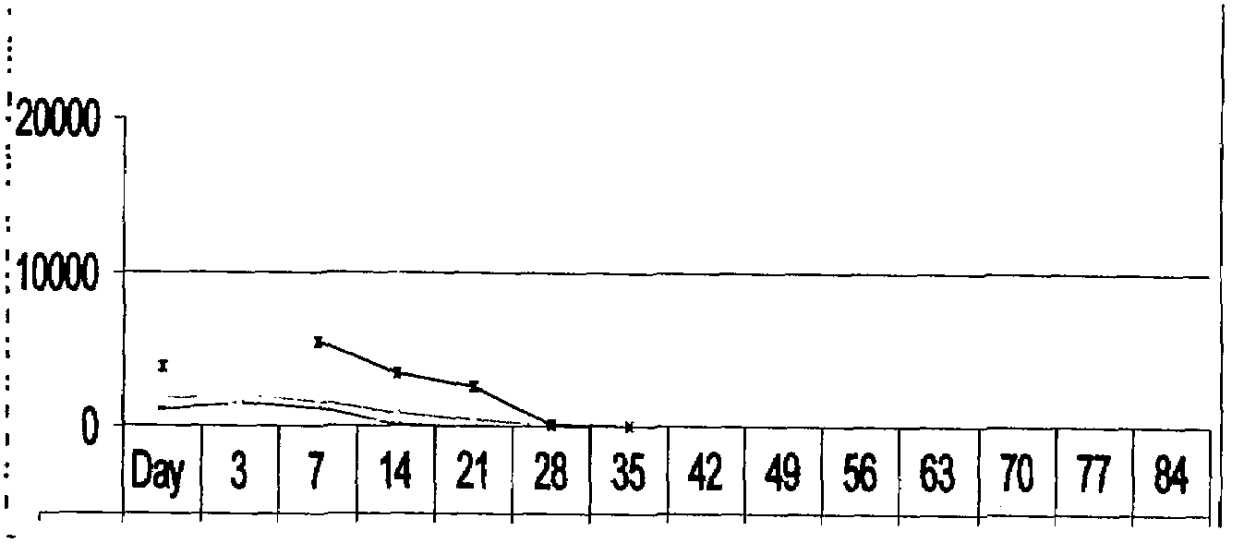

Fig. 1. Illustrates the initial serum hCG concentrations and its pattern during th follow up period in 23 patients treated with methotrexate

Table VI : clinical and operative details of women who required surgey after MTX therapy.

	S. hCG		S. progest.	Mass size (cm)		
1	993	1098	0.3	1.0	Un-ruptured	Salpingectomy
2	1875	1960	12.27	4.0	Un-ruptured	Salpingectomy
3	9596	9850	7.53	1.2	Un-ruptured	Salpingectomy
4	4147	4366	3.7	3.0	Un-ruptured	Salpingectomy
Mean	4148.3	4318.5	5.9	2.3		
SD	3867.9	3938.4	5.1	1.47		

Table VII : Details of the six patients treated with two doses methotrexate.

	D1	D7	Mass size (cm)	Resolution time (days)
1	4713	6551	2.1	62
2	4860	4400	4.2	48
3	9789	11760	1.9	55
4	1944	3371	1.9	52
5	3880	5456	2.8	32
6	1909	2880	1.9	38
Mean	4582.2	5736.3	2.47	47.8
± SD	2822.8	3242.4	0.92	11.1

D1 = Day 1, D7 = Day 7

Table VIII : Comparison between patients receiving one methotrexate dose and those receiving two doses in the treated group.

	1 dose	2 doses	P
HCG (mIU/ml)	2995.75 ± 3494.98	4515.8 ± 2890.6	0.325
Progesterone (ng/ml)	7.05 ± 8.5	13.82 ± 22.8	0.26
Mass size (cms)	2.02 ± 0.77	2.47 ± 0.92	0.658
Resolution time (days)	33.15 ± 14.56	47.8 ± 11.11	0.142
Gestational age (days)	48.2 ± 10.57	48.2 ± 12.4	0.19
Free peritoneal fluid	13 (46.4%)	1 (16.7%)	

Table IX : Comparison of results between intravenous and intramuscular routes of MTX for the treatment of un-ruptured ectopic pregnancy.

	Current study	Khaled B (17)	Stika et al (18)	Stovall & Ling(7)	Glock et al(14)
No of women	34	30	50	120	35
Age (years)	27.9 ± 5.9	27.1 ± 5.6	32 ± 5.6	26.1 ± 6.2	30.8 ± 0.9
Parity	2.03 ± 2.29	1.4 ± 1.3	0.8 ± 1.3	0.97 ± 1.0	0.5 ± 0.2
HCG level mIU/ml	3247.53±3408.1	2209 ± 1381	1896 ± 2399	3950.6 ± 1193	1388.1 ± 464
Adnexal masses detected by USS	28 (82.4%)	23 (76.7 %)	13 (26 %)	113 (94.3 %)	6 (17.1 %)
No of doses:					
1 dose MTX	28 (82.4%)	24 (80 %)	39 (78 %)	116 (96.7 %)	33 (94.3 %)
2 doses MTX	6 (17.6%)	5 (16.7 %)	10 (20 %)	4 (3.3 %)	2 (5.7 %)
3 doses MTX	0	1 (3.3 %)	1 (2 %)	0	0
Success rate:					
1 dose	28 (82.4%)	22 (73.3 %)	32 (64 %)	1&2 doses	30 (85.7 %)
1-3 doses	30 (88.2%) (2 doses only)	26 (86.7 %)	39 (78 %)	together 113 (94.2 %)	2 doses 0% success
Resolution time (days)	35.1±12.8	32.5 ± 17	26.9 ± 17	35.5 ± 12	23.1 ± 2.9
failure rate	4/34 (11.8%)	4/30 (13.3 %)	11/50 (22 %)	7/120 (5.8 %)	5/35 (14.3 %)

COST EFFECIVENESS

The policy of offering methotrexate as the front line of treatment for early un-ruptured ectopic pregnancy results in cost saving of approximately 2500 SR per treated patient (compared to exploratory laparotomy in a private hospital in Al Madinah Al Munawarah city). In the United States, it is approximately $3000 per treated patient [19]. The psychological cost is often overlooked as it's not generally viewed in the same way as pregnancy loss. It would seem that the woman has similar grief reactions to those with miscarriages but have the additional trauma of loosing one tube and the potential future reduction of fertility. Questioning women, most of them prefer non surgical treatment of ectopic pregnancy.

CONCLUSION

Expectant and medical management for ectopic pregnancy are effective options in selected cases as long as facilities for monitoring are available.

Single dose of intravenous methotrexate is well tolerated, cost-saving, non-surgical fallopian tube sparing treatment for un-ruptured ectopic pregnancy. Methotrexate treatment should be offered as the first line of treatment to those women with ectopic gestations in centers where quick facilities for the diagnosis are available.

The initial serum chorionic gonadotrophin concentration is the best prognostic indicator for treatment success in these women treated with methotrexate according to the single-dose protocol.

Pain developing after methotrexate therapy for ectopic pregnancy should not be the only indication for surgical intervention.

The prognostic value of the proposed factors appears to be directly related to their association with serum hCG concentration. These women should be well evaluated, and methotrexate is still a treatment option.

These results can be used to counsel women with ectopic pregnancies regarding the likelihood of successful treatment with single-dose intravenous methotrexate.

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