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Original Research Article

Management outcomes of ectopic pregnancy depending on different treatment modalities: a cohort study

Shawqi H. Alawdi^{1,2}, Mayada Roumieh^{3,4}, Marwan Alhalabi^{3,4,5*}

¹Department of Pharmacology, Faculty of Pharmacy, International University for Science and Technology (IUST), Syria

²Department of Pharmacology, Faculty of Medicine, Tamar University, Yemen

³Department of OBGYN, ⁴Maternity Hospital of OBGYN Faculty of Medicine, Damascus University, Syria

⁵Division of Reproductive Medicine, Embryology and Genetics, Faculty of Medicine, Damascus University, Syria

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***Correspondence:**

Dr. Marwan Alhalabi,

E-mail: profalhalabi@gmail.com

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ABSTRACT

Background: Ectopic pregnancy is the most common cause of maternal morbidity and mortality during the first trimester of pregnancy. The present study aimed to review and evaluate the management outcomes of ectopic pregnancy in Damascus University Maternity Hospital, Syria.

Methods: A retrospective cohort study was performed on women referring to Damascus University Hospital of Obstetrics and Gynecology (OBGYN) for ectopic pregnancy. Patients were assigned into groups by method of treatment: expectant management (Group 1), single-dose methotrexate regimen (Group 2), two-dose methotrexate regimen (Group 3), and surgical intervention (Group 4). Parameters assessed were risk factors for ectopic pregnancies, transvaginal ultrasonography findings, serum human chorionic gonadotropin (hCG) levels on Days 0, 4, 7, and types of surgical intervention in women that underwent any surgical intervention. A treatment modality was considered successful when hCG levels declined to less than 5 mIU/L without further administration of methotrexate dose or need for surgery.

Results: Seventy-seven women with ectopic pregnancy were admitted to the hospital during the study period. Groups 1, 2, 3, and 4 constituted 20.8%, 13.0%, 6.5% and 59.7% of the patients respectively. The most common encountered risk factors for ectopic pregnancy in the patients were history of previous intra-abdominal or pelvic surgery (57.1%) and history of miscarriage (41.6%). A statistically significant difference in the serum hCG concentrations measured on day 0, day 4, and day 7 were observed between the groups.

Conclusions: The success rate in ectopic pregnancy treatment was 56.25% for the expectant management, 70% for the single-dose methotrexate regimen, and 40% for two-dose methotrexate regimen.

Keywords: Tubal pregnancy, Ectopic pregnancy, Methotrexate, hCG

INTRODUCTION

Ectopic pregnancy is almost the most common cause of maternal morbidity and mortality during the first trimester of pregnancy.¹ It involves implantation and subsequent development of the embryo at an abnormal site other than the normal site of within the endometrium.^{2,3} The embryo

is not able to grow normally when it is implanted in other places than the uterus which is designed to accommodate the embryo and its growth needs. Hence, it will almost results in abortion or rupture.⁴ Treatment of ectopic pregnancy includes three approaches: surgical, medical, and expectant management. Expectant management is an option for hemodynamically stable women with minimal

symptoms, small ectopic mass, no rupture findings on transvaginal ultrasonography, and compliant with follow-up at least weekly with serial serum hCG.^{1,5} Medical treatment with methotrexate, a folinic acid antagonist that inhibits nucleic acid synthesis by deactivating dihydrofolate reductase enzyme, is the preferred cost-effective choice for women with unruptured ectopic pregnancy.⁶ Surgical intervention is offered for hemodynamically unstable patients or patients with acute abdominal findings of ruptured ectopic pregnancy.⁷

In this present study, we reviewed all ectopic pregnancy cases admitted to Damascus University Hospital of OBGYN, Syria between January 1, 2019 and December 31, 2019. The outcomes of the four treatment modalities of ectopic pregnancy were compared.

METHODS

Study design and population

This retrospective cohort study reviewed all diagnosed cases with ectopic pregnancy in Damascus University Maternity Hospital of OBGYN, Syria for the period between January, 2019 and December, 2019. The study was approved by the institutional ethics committee. Data on the ectopic pregnancy treatment were collected from the hospital medical records and patients' files and were analyzed retrospectively. Sociodemographic characteristics included age, smoking, clinical presentation, gestational age, gravidity, parity, history of using contraceptive methods, history of ectopic pregnancy, history of previous pelvic or abdominal surgery, history of infertility treatment, history of miscarriage, transvaginal ultrasonography findings (gestational sac, ectopic mass appearance, positive fetal cardiac activity), serum human chorionic gonadotrophins (hCG) levels on day 0, day 4, and day 7, and the duration of hospital stay for women who underwent surgical interventions for treatment of ectopic pregnancy.

Diagnosis and treatment protocol

Women were diagnosed with ectopic pregnancy when they had positive transvaginal ultrasonography findings (gestational sac, ectopic mass appearance, and positive fetal cardiac activity) and a persistent increase in serial serum hCG levels without the presence of intrauterine pregnancy. Patients were treated using expectant management when spontaneous resorption of ectopic pregnancy was expected in hemodynamically stable patients by a greater than 15% decrease in their daily serial serum hCG levels. Medical management with methotrexate was given for hemodynamically stable patients who had less than 50% increase in their serum hCG levels over two consecutive days or patients whose hCG levels had plateaued. Methotrexate intramuscular dose (50 mg/m² body surface area) was administered and serial serum hCG levels were measured on day 0, day 4, and day 7. If the hCG levels on the 7th day were at least

15% lower than the levels on the 4th day, then serial measurements of hCG at a weekly basis were performed until the levels plunged to values less than 5 mIU/L. Single-dose methotrexate regimen was considered successful when hCG levels declined to less than 5 mIU/L without further administration of methotrexate or need for surgery. If the hCG levels were decreased by less than 15% between day 4 and day 7, a second dose of methotrexate was offered. For the two-dose regimen, two doses of methotrexate (50 mg/m² body surface area) were used on day 0 and day 4 for patients with high hCG levels (example- hCG >5000 mIU/mL + ectopic cardiac activity). If the hCG levels were dropped by $\geq 15\%$ from day 4 to day 7, then serial measurements of hCG were followed at a weekly basis until the levels plunged into values less than 5 mIU/L. A third methotrexate dose was required if the hCG levels were decreased by less than 15% between the fourth and seventh day. Moreover, if the hCG levels were not declined by at least 15% between day 7 and day 11, surgical intervention was required.

Statistical analysis

Statistical analysis was performed using Statistical package for social sciences) SPSS 15.0 software (Chicago, Illinois, USA). One-way analysis of variance (ANOVA) was used to test differences between different groups followed by Tukey-Kramer or Bonferroni post-hoc tests for multiple comparisons according to the distribution type of variables in these groups. The categorical variables were presented as the number of cases and the percentage, and the continuous variables were presented as mean \pm standard deviation (SD). Statistical significance was set at $p < 0.05$.

RESULTS

A total of 77 cases with ectopic pregnancy were diagnosed in Damascus University Hospital of OBGYN. According to the clinical protocol of the management, 16 cases (20.8%) of the 77 patients were treated using expectant management (Group 1), 10 patients (13.0%) were treated with single-dose methotrexate regimen (Group 2), 5 patients (6.5%) were treated with two-dose methotrexate regimen (Group 3), and the remaining 46 (59.7%) patients underwent surgical intervention (Group 4). The demographic characteristics and the ultrasonography findings of the patients with ectopic pregnancy are presented in Table 1.

Patients' age ranged between 16 and 40 years, and most cases of ectopic pregnancy patients aged between 20-40 years (92.3%) with higher frequency of distribution between 30-40 years (48.1%). Smoking habit was found in about 14.3% of women diagnosed with ectopic pregnancy while both alcohol and smoking habits were found only in 1.3% of the patients. No significant difference was observed in the age of patients between the groups.

The most frequent main complaint among ectopic pregnancy patients was pain with vaginal bleeding in 48.1% of the patients. Also, 22.1% of the patients had abdominal pain as the main complaint. However, patients in the four groups did not differ significantly in the symptoms associated with ectopic pregnancy.

The most common encountered risk factors of ectopic pregnancy among patients were the history of previous intra-abdominal or pelvic surgery (57.1%) followed by the history of miscarriage (41.6%). The history of ectopic

pregnancy was found only in 2.6% of the patients. Smoking was also found in 14.3% of the patients. No significant differences of the risk factors were observed between groups. Transvaginal ultrasonography revealed that most patients had gestational sac plus ectopic mass appearance (90.9%). Other less frequent findings were either only an ectopic mass or a gestational sac. Similarly, all the four groups did not differ significantly in terms of these diagnostic ultrasonography findings.

Table 1: Clinical presentation, history, and ultrasonography findings in patients with ectopic pregnancy.

	Total (n=77)	Group 1 Expectant management (n=16)	Group 2 Single-dose methotrexate (n=10)	Group 3 Two-dose methotrexate (n=5)	Group 4 Surgical intervention (n=46)	P value
Age	28.1±6.22	25.88±7.47	28.60±6.47	25.60±4.39	29.02±5.76	0.272
Clinical presentation (%)						0.189
Pain	37 (48.1)	6 (37.5)	1(10)	0(0)	10(21.7)	
Vaginal bleeding	17 (22.1)	0(0)	1(10)	1(20)	3(6.5)	
Pain + vaginal bleeding	9 (11.7)	8(50)	4(40)	1(20)	24(52.2)	
Pain + amenorrhea	6 (7.8)	0(0)	0(0)	2(40)	4(8.7)	
Vaginal bleeding + amenorrhea	5 (6.5)	1(6.3)	1(10)	0(0)	1(2.2)	
Pain + vaginal bleeding + amenorrhea	3 (3.9)	1(6.3)	3(30)	1(20)	4(8.7)	
History (%)						
Previous intra-abdominal surgery	44 (57.1)	8 (50)	8(80)	3(60)	25(54.3)	0.466
History of infertility treatment	0(0)	0(0)	0(0)	0(0)	0(0)	0
History of ectopic pregnancy	2 (2.6)	0(0)	0(0)	0(0)	2(4.3)	0.721
History of miscarriage	32 (41.6)	7(43.8)	5(50)	3(60)	18(39.1)	0.712
Smoking	11(14.3)	1(6.3)	3(30)	2(40)	5(10.9)	0.900
Gestational age	53.9±27.9	49±13.53	57±18.61	42±11.07	56.2±33.83	0.609
Findings on USG (%)						0.233
Gestational sac	1 (1.3)	1 (6.3)	0(0)	0(0)	0(0)	
Ectopic mass appearance	3 (3.9)	1 (6.3)	1(10)	1(20)	0(0)	
Gestational sac + ectopic mass appearance	70 (90.9)	14(87.5)	9(90)	3(60)	44(95.7)	
Gestational sac + ectopic mass appearance + positive fetal cardiac activity	3 (3.9)	0(0)	0(0)	1(20)	2(4.3)	

Table 2: The hCG levels in all four groups on day 0, day 4, and day 7.

	Group 1 Expectant management (n=16)	Group 2 Single-dose methotrexate (n=10)	Group 3 Two-dose methotrexate (n=5)	Group 4 Surgical intervention (n=46)	P value
Day 0	1276±912.2 ^{1,2,3}	2461±995.5 ⁴	2652±831.5 ^{2,5}	8432±6611 ^{3,4}	<0.001*
Day 4	1152±672.0 ^{1,2}	2241±877.4	2128.±617.1	-	0.002*
Day 7	963±550.7	1654±870.8	1752±705.2	-	0.024

* statistically significant between groups; ¹: group 1 versus group 2, ²: group 1 versus group 3, ³: group 1 versus group 4, ⁴: group 2 versus group 4, ⁵: group 3 versus group 4.

Table 3: Changes in the hCG levels from day 0 to day 4 and from day 4 to day 7 after methotrexate administration.

	Group 1 Expectant management (n=16)	Group 2 Single-dose methotrexate (n=10)	Group 3 Two-dose methotrexate (n=5)	P value
Day 4-0	124±112.5 (9.72%)	220±129.5 (8.94%)	524±254.7 (19.77%)	0.247
Day 7-0	189±177.1 (16.41%)	587±260.7 ¹ (26.19%)	376±154.6 (17.67%)	0.023*

* statistically significant ¹: group 1 versus group 2.

Table 4: Differences between the hCG levels from day 0 to day 4 in ectopic pregnancy patients.

	Group 1 Expectant management (%)	Group 2 Single-dose methotrexate (%)	Group 3 Two-dose methotrexate (%)	Total (%)
Negative value	12 (75)	8 (80)	5 (100)	25 (80.6)
Positive value	4 (25)	2 (20)	0 (0)	6 (19.4)
Total	16 (100)	10(100)	5 (100)	31 (100)

Table 5: Differences between the hCG levels from day 4 to day 7 in ectopic pregnancy patients.

	Group 1 Expectant management (n=16) (%)	Group 2 Single-dose methotrexate (n=10) (%)	Group 3 Two-dose methotrexate (n=5) (%)	Total (n=77) (%)
Negative value	14 (87.5)	9 (90)	5 (100)	28 (90.3)
Positive value	2 (12.5)	1 (10)	0 (0)	3 (9.7)
Total	16 (100)	10 (100)	5 (100)	31 (100)

The measured hCG concentrations in the four groups on Day 0, Day 4, and Day 7 is shown in Table 2.

Table 6: The need for surgical intervention.

Modality	N (%)
Surgery	46 (59.7)
Expectant management + surgery	9 (11.7)
Expectant management	7 (9.1)
Single-dose methotrexate	7 (9.1)
Two-dose methotrexate	3 (3.9)
Single-dose methotrexate + surgery	3 (3.9)
Two-dose methotrexate + surgery	2 (2.6)

Serum hCG levels decreased between day 0 and day 4 in 75% of the patients who were offered the expectant management (group 1), in 80% of the patients who received a single methotrexate dose (group 2), and in 100% of the patients who received two or more doses of methotrexate (group 3). Moreover, the hCG concentrations decreased on day 7 in comparison to day 4 in 87.5%, 90%, and 100% in groups 1, 2 and 3 respectively. The complete plunge in hCG levels was observed in 80.6% between day 4 and day 0, and 90.3% between day 7 and day 4 in all patients with ectopic pregnancy (Tables 4 and 5).

The need for surgical intervention among patients with ectopic pregnancy is summarized in Table 6. More than half (56.2%) of the patients treated with expectant

management needed a surgical intervention. About 30% of the women who had received the single-dose methotrexate regimen also needed a surgical intervention. Moreover, 40% of the patients treated with two-dose methotrexate regimen needed a surgical intervention.

Table 7: Types of surgical intervention.

Modality	N (%)
Salpingectomy total	59 (76.6)
No surgery performed	16 (20.8)
Salpingostomy partial	1 (1.3)
Transampullary expression or milk-out	1 (1.3)

In terms of surgical procedure types, total salpingectomy was performed for 76.6% of the patients with ectopic pregnancy who needed a surgical intervention.

The lowest percentage (1.3%) of patients received either partial salpingostomy or trans-ampullary expression (milking). On the other hand, only 20.8% of the patients did not need surgical intervention. Types of surgical interventions are summarized in Table 7.

DISCUSSION

The present study investigated the outcomes of ectopic pregnancy in patients who attended the Damascus University Hospital of OBGYN, Syria. Management of ectopic pregnancy depends on the hemodynamic stability

of the patient, the hCG levels, as well as the size of the ectopic pregnancy and the presence of fetal cardiac activity, in addition to the fertility needs and compliance with long-term follow-up.¹

The average level of the hCG in patients treated with expectant management was 1276 mIU/L in the present study. Expectant management is more preferred over medical management with methotrexate when the initial serum hCG concentrations are less than 1500 mIU/L in the unruptured tubal ectopic pregnancy.^{8,9} More than half (56.2%) of the patients in the present study treated with expectant management needed further surgical intervention, and spontaneous resolution occurred only in 43.8% of these patients. These high rates could be attributed to the fact that patients with ectopic pregnancy are usually referred to our tertiary hospital for medical treatment or surgical intervention.

Medical management with methotrexate is regarded an effective treatment modality for ectopic pregnancy patients with appropriate criteria for medical management including hemodynamic stability and fertility demand. In the present study, the single-dose methotrexate regimen was associated with 8.94% decrease in hCG levels between day 4 and day 0 while the two-dose methotrexate regimen was associated with 19.77% decrease in hCG levels. Between day 4 and day 7, the decrease in hCG levels was also further 26.19% in single-dose methotrexate regimen and 17.67% in two-dose methotrexate regimen. The changes in hCG levels between day 4 and day 7 were used to measure the success of methotrexate therapy and the changes in hCG levels between day 4 and day 0 were used to predict the success of methotrexate therapy. These changes ranged in the literature from 9.08% to 22.0% between day 0 and day 4.¹⁰⁻¹³ Other studies reported that treatment success might not be predicted by the decrease in hCG levels.⁷

In this study, 70% of the women who had received the single-dose methotrexate regimen and 40% of the patients treated with two-dose methotrexate regimen needed no further surgical interventions. The success rate of the single-dose methotrexate regimen was reported in the literature to be between 52% and 94% which goes in line with the results of the present study.^{14,15} The lower success rate of the two-dose methotrexate regimen (40%) found in the present study could be explained by the high hCG levels in patients treated with two-dose methotrexate regimen (average = 2652 mIU/L). In the literature, serum levels of hCG have been correlated with the success rate of methotrexate medical therapy which supports the explanation for our findings.^{7,11,14,16} In addition, the American Society for Reproductive Medicine Guidelines suggest that medical treatment with single-dose methotrexate regimen fails at high initial serum hCG levels.

Moreover, no significant difference was observed in the present study between the success rates of the single-dose

and two-dose methotrexate regimens (40% and 30%, respectively). These results are in accordance with similar findings reported in previous studies including a prospective randomized trial.¹⁷⁻¹⁹ These observations suggest that the single-dose methotrexate regimen should be considered when the side effects preclude the use of multiple-dose methotrexate regimens.

Limitations

Our limitations included a relatively small sample size collected through simple sampling in our university hospital with the data collection also done retrospectively. Our hospital is known to be a center for referral of clinically severe cases in Obstetrics and Gynecology and such is the case in our data being more skewed towards requiring surgical intervention. Prospective randomized studies involving a larger number of patients are needed to substantiate our findings.

CONCLUSION

The results of the present study showed that success rate of the expectant management was 56.25%, for the single-dose methotrexate regimen was 70%, and in the two-dose methotrexate regimen was 40% of the patients with ectopic pregnancy. These rates were correlated with the initial concentrations of serum hCG concentrations. The changes in hCG levels between day 0 and day 4 after receiving methotrexate may predict the outcomes of therapy.

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