Original Article

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A Clinical Experience of Ectopic Pregnancies with Initial Free Intraperitoneal Fluid

Obstetrics and Gynaecology Section

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ABSTRACT

Introduction: Extra-uterine pregnancy or Ectopic Pregnancy (EP) is a major health problem for pregnant women, presenting as a potentially life-threatening emergency in the first trimester. There are three major options for the treatment of EP: expectant management, surgical treatment and medical management. The presence of free intraperitoneal fluid in EP-diagnosed patients is crucial for treatment planning and evaluation.

Aim: To compare the outcomes of both the expectant management and medical treatment with methotrexate (MTX) in ectopic pregnancies with free intraperitoneal fluid.

Materials and Methods: This retrospective cohort study included a total of 91 ectopic pregnancies with or without rupture in which the women had initial free intraperitoneal fluid and were haemodynamically stable. Serial β-HCG measurements were used to assess the outcome of expectant management and medical treatment with MTX. For the statistical analysis, the SPSS statistical software package, version 22.0 (Chicago, IL, USA), was used. For the quantitative variables that were not distributed normally, the Kruskal-Wallis test and the Mann-Whitney U test were performed for the evaluation of differences between the groups.

Results: It was observed that the success rate with expectant management was 81% (initial β HCG concentration 626±443 mIU/mL). With a single dose of MTX, it was 76% (initial β HCG concentration 2124±1647 mIU/mL) and with a total single or double dose of MTX, it was 88% (initial β HCG concentration 2252±78 mIU/mL) from among EP with or without rupture in women with initial free intraperitoneal fluid during diagnosis. There was no significant difference between the groups with regard to ultrasonography findings.

Conclusion: Expectant management or medical treatment with methotrexate should be the first line treatment for ectopic pregnancies with initial free intraperitoneal fluid, albeit with rupture, in patients who are haemodynamically stable, along with β-HCG follow-up.

Keywords: Chorionic Gonadotropin, Haemoperitoneum, Methotrexate

INTRODUCTION

Extra-uterine pregnancy or Ectopic Pregnancy (EP) is a major health problem for pregnant women, presenting as a potentially life-threatening emergency in the first trimester [1]. EP occurs in approximately 1-2% of all pregnancies [2]. Serial beta β Human Chorionic Gonadotropin (β-HCG) measurements and advances in Transvaginal Ultrasonography (TVU) contribute to the early diagnosis of an EP before rupture occurs by providing increased clinical suspicion and by bearing the possibility in mind more frequently [3]. Early diagnosis provides the opportunity of more widespread use of medical therapy rather than surgery. There are three major options for the treatment of EP: expectant management, surgical treatment and medical management.

Expectant management should only be considered for women with low (≤200 mIU/mL) and decreasing serum β-HCG levels [4].

Laparoscopic surgery is the standard surgical approach for EP. Laparotomy can be preferable for patients who are haemodynamically unstable with intra-abdominal bleeding [5]. There are three choices of surgical approach for tubal pregnancy: salpingostomy, salpingotomy and salpingectomy [6]. Partial or total oophorectomy is commonly performed for ovarian EP [7].

Medical treatment of an unruptured EP using intramuscular Methotrexate (MTX) was first attempted by Tanaka et al., in 1982 [8]. Since the first successful trial of MTX treatment, it has become increasingly popular worldwide. It is easier to apply and is more cost-effective compared to surgery. In addition, MTX treatment has shown comparable success rates, safety and fertility preservations with surgery since single-dose and multi-dose MTX therapy protocols have been developed. The optimal treatment protocol has been discussed repeatedly in the literature [9-11]. The single-dose protocol is more popular and a more commonly used regimen worldwide, with success rates of 52-94% [12]. The other agents used for medical management protocols in EP are potassium chloride, hyperosmolar glucose, dactinomycin, prostaglandins and RU 486.

Most of the previously published protocols for the treatment of EP have restricted the use of systemic MTX based on serum chorionic gonadotropin concentrations usually more than 5000 or 10,000 mIU/mL and in women with a gestational mass larger than 3 to 4cm in size [13,14]. These therapeutic limitations are determined based on the success rate. Absolute contraindications for MTX treatment are intrauterine pregnancy, immunodeficiency, moderate to severe anemia, leukopenia or thrombocytopenia, sensitivity to MTX, active pulmonary or peptic ulcer disease, clinically important hepatic or renal dysfunction and breast feeding [9]. Relative contraindications for MTX therapy are positive fetal cardiac activity, high initial β-HCG concentrations (>5,000 mIU/mL), gestational mass >4 cm size, refusal to accept blood transfusion and inability to participate in follow-up [9]. Atypical localization (interstitial, cervical, ovarian or cesarean section scar) is also a relative contraindication, particularly for multiple dose MTX regimens. There are other studies indicating safety and similar efficacy of the use of systemic and local MTX treatment in Cesarean scar pregnancies [15,16].

The presence of free intraperitoneal fluid in EP-diagnosed patients is crucial for treatment planning and evaluation. It has been described as a relative contraindication for MTX regimens in the early years of the use of MTX for EP management. Currently, it does not constitute a contraindication for MTX regimens unless there is haemodynamic instability [9].

AIM

In this study, treatment success of the expectant management or medical treatment with methotrexate was assessed among patients with ectopic pregnancy in whom initial free intraperitoneal fluid was detected.

MATERIALS AND METHODS

The present retrospective study was conducted in the Department of Obstetrics and Gynaecology of Fatih Sultan Mehmet Training and Research Hospital. Ethical approval was obtained and reviewed by the human ethics committee for use of the hospital data of patients who were diagnosed with EP between January 2008 and June 2015. A total of 91 patients with EP who had initial free intraperitoneal fluid were included in the study.

The diagnosis of EP was made by repeated β-HCG level measurements and TVU imaging. Patients suspected of having EP if they had serum b-HCG levels that had low doubling rates with β-HCG rise <53% or persistent values [17]. TVU was used to determine the EP with at least one of the following findings: direct visualization of an extra-uterine gestational sac with or without intrauterine pseudo-sac; and quantitative serum β-HCG greater than the discriminatory zone unless an intrauterine gestational sac was observed. The existence or absence of free intraperitoneal fluid and blood clots on TVU was noted.

All the TVU examinations were performed by specialist gynaecologists. Haemoperitoneum was determined by measuring the deepest antero-posterior size of the posterior uterus on the mid-sagittal plane involving the uterus, rectouterine pouch, pelvis and abdomen. Patients who had signs of haemodynamic instability (tachycardia, hypotension, confusion) and signs of acute abdomen (pain with palpation and rebound tenderness) underwent emergency surgery. Other patients with free intraperitoneal fluid with or without blood clots were treated expectantly or with MTX administration.

Uterine curettage was performed to patients whose pregnancy localization was unknown. β-HCG was repeated after uterine curettage. Expectant management or MTX treatment was performed according to whether there is persistence or decrease in β-HCG levels. The results of histopathologic examination were used for definitive diagnosis. Histological diagnosis was performed in the absence of trophoblastic tissue.

The selection criteria for expectant management were presence of any intact extra-uterine gestational sac or suspected adnexal mass or when nothing was seen on TVU examination with spontaneous daily decreases in serum β-HCG levels. Single dose MTX treatment was performed if the patient had increasing serum β-HCG concentrations or did not experience a proper decrease (<10% decrease between any two measurements). The exclusion criteria for MTX treatment were abnormal haematologic, renal or hepatic laboratory results, hypersensitivity to MTX, immunodeficiency, active pulmonary disease, peptic ulcer disease and breast feeding.

Treatment success was defined as spontaneous decrease every 48 hours in β-HCG levels by >10% for the expectant management group. MTX administration or surgery was performed as indicated after a repeat TVU if the β-HCG level was not properly decreasing or if the clinical situation of the patient changed. MTX treatment success was defined as >15% decrease in β-HCG levels between days four and seven. Whenever the β-HCG level failed to decrease by 15% between days 4 and 7 in the single dose MTX group, an additional injection of MTX was administered or laparoscopy was performed according to the TVU examination and the clinical situation. All the patients were followed up weekly until negative β-HCG values were attained.

The above mentioned information is the protocol followed in the hospital and they have been described for the purpose of understanding the patient selection and the procedure of patient management. Being a retrospective study, all the relevant data were collected from the hospital database.

For the purpose of the study five groups were formed as; successful single dose MTX treatment, successful second dose MTX treatment, surgery during MTX treatment, successful expectant management and unsuccessful expectant management groups.

STATISTICAL ANALSIS

For the statistical analysis, the SPSS statistical software package, version 22.0 (Chicago, IL, USA), was used. The Shapiro-Wilk test was performed to determine whether the data were sampled from a normal distribution. Descriptive data were statistically described in terms of range, means±SDs, frequencies (number of cases), and percentages when appropriate. For the quantitative variables that were not distributed normally, the Kruskal-Wallis test and the Mann-Whitney U test were performed for the evaluation of differences between the groups. Pearson's chi-square test was used to compare means between nonparametric and parametric values. A probability value of <0.05 was considered statistically significant.

RESULTS

A total of 91 EP aged between 19-50 years (30.76±6.52) with initial free intraperitoneal fluid were retrospectively identified between January 2008 and June 2015. A total of 54 patients who had no contraindications for MTX treatment were treated with single dose MTX and 37 patients receive expectant management. [Table/Fig-1] presents the clinical and demographic variables of the study participants. The mean age of the patients was 30.76 ± 6.52 (19-50) years.

The gestational age, initial serum β-HCG level and negative β-HCG values during follow-up in the expectant management group were significantly lower than in the successful single dose and second dose MTX treatment groups (p<0.05). The initial HCG concentrations of patients who had single or second dose of MTX were found to be significantly higher than those in the expectant management group, with an HCG concentration of 2252±78 mIU/mL. The TVU evaluation results of the patients are shown in [Table/Fig-2]. There was no significant difference between the groups on the TVU findings.

We found that the success rate with single dose MTX was 76%, with either single or second dose MTX, it was 88% and with expectant management, it was 81% [Table/Fig-1].

Surgical treatment was needed in 2 of 37 expectant management patients and in 6 of 54 single dose MTX-treated patients. Five patients were administered single dose MTX in the failed expectant management group. In the medical treatment group, surgery was performed during first and second doses of MTX in 4 and 2 patients, respectively.

DISCUSSION

In the present study, comparing the treatment outcomes of EP in women with free intraperitoneal fluid, we showed that both expectant management and single-dose MTX treatment could be successfully administered to haemodynamically stable patients although free intraperitoneal fluid was present.

Ultrasonographically detected free intraperitoneal fluid has been determined to be a relative contraindication for MTX treatment in the past [18,19]. In 2008, the American Society for Reproductive Medicine (ASRM) Practice Committee stated that existence of free intraperitoneal fluid was no longer a contraindication but a criterion for predicting failure of medical treatment with MTX [9]. In the 2013 ASRM committee report, as distinct from previous reports, having a ruptured EP and haemodynamic instability were separately added back to the absolute contraindications for MTX treatment

Variable	MTX single dose success group (n = 41)	MTX second dose success group (n = 7)	MTX failure group (n = 6)	Expectant management success group (n =30)	Expectant management failure group (n = 7)	p-value
[1]Age (year), mean (±SD)	30.32 (6.31)	31.71 (4.5)	25.83 (5.56)	31.53 (6.96)	33.29 (7.34)	0.291
[1]BMI (kg/m^2), mean (±SD)	29.44 (3)	28.86 (3.48)	28.17 (4.79)	29.17 (3.33)	28.57 (4.96)	0.90
[1]Parity, mean (±SD)	0.8 (0.93)	1 (1.15)	0.83 (0.75)	1.63 (1.43)	0.43 (0.79)	0.80
[1]Abortus, mean (±SD)	0.49 (0.78)	0.43 (0.53)	0.5 (0.84)	0.37 (0.67)	0.57 (0.79)	0.897
[1] Previous Ectopic Pregnancy, mean (±SD)	0.15 (0.53)	0.11 (0.33)	0.17 (0.41)	0.13 (0.43)	0.14 (0.38)	0.789
[1]Gestational age (weeks), mean (±SD)	5.98 (1.39)	7.29 (2.06)	5.83 (1.83)	4.53 (0.68)	5.29 (0.95)	0.001**
[1]B-HCG level (mIU/mL), mean (±SD)	2124 (1647)	3006 (1523)	2477 (1397)	626 (443)	694 (496)	0.001**
[1] Weeks until negative B-HCG values reached, mean (±SD)	5. 88 (1.99)	8.29 (0.49)	4.67 (1.37)	4.8 (1.37)	6.14 (1.21)	0.001**
Succes rates[#] (n,%)	41/54, 76%	[#]48/54, 88.8%		30/37, 81%		

[Table/Fig-1]: Clinical and demographic variables of the patients.
[1]Kruskall-Wallis test [2]Chi-square test. *p<0.05 **p<0.01. [#]Total success rates of single and second dose MTX treatment

Findings	MTX single dose success group (n = 41)	MTX second dose success group (n = 7)	MTX failure group (n =6)	Expectant management success group(n =30)	Expectant management failure group (n = 7)	p-value
[1]Endometrial thickness (mm), mean (±SD)	9.24 (4.45)	10 (4.65)	10.33 (8.29)	8.43 (3.26)	8.57 (4.24)	0.921
[1]Size of free peritoneal fluid (mm), mean (±SD)	21.78 (9.61) (12-50)	24.86 (3.34) (16-40)	23 (11.3) (12-39)	21.07 (8.42) (11-45)	19.29 (8.83) (10-47)	0.200
[2]Intrauterine device present, n (%)	3 (7.3)	2 (28.6)	1 (16.7)	3 (10)	0 (0)	0.390
[2]Presence of ectopic pregnancy or adnexal mass, n (%)	23 (56.1)	6 (85.7)	4 (66.7)			0.525
[1]Size of ectopic pregnancy or adnexal mass (mm), mean (±SD)	24.52 (10.44)	26.2 (6.45)	27.75 (7.5)			0.52

[Table/Fig-2]: Transvaginal ultrasonography findings of the patients.
[1]Kruskall-Wallis test. [2]Chi-square test. *p<0.05. **p<0.01

[20]. Considering the two different ASRM committee reports we think that there is an inconsistency particularly in patients who are haemodynamically stable but with free intraperitoneal fluid. We designed this study to examine whether the existence of free intraperitoneal fluid was an absolute or relative contraindication for MTX treatment in haemodynamically stable patients with ectopic pregnancy, albeit with rupture or not.

Ruptured ovarian cysts and EP are the most common causes of haemoperitoneum. Hepatic, splenic, vascular or coagulopathic aetiologies can play roles in haemoperitoneum [21]. Women in their reproductive periods may have trace amounts of physiologic free pelvic fluid [22].

Ultrasonographically detected free peritoneal fluid can consist of blood in EP. The source of the blood could be tubal abortion or a ruptured EP. There is no direct laboratory test or any non-invasive method to distinguish between ruptured pregnancy and tubal abortion as the cause of the free fluid in haemodynamically stable patients. Currently, invasive methods, such as culdocentesis (Douglas puncture) and diagnostic peritoneal lavage are not used very often for the management of EP. Laparoscopy is widely used in diagnosing and treating EP. Laparoscopy was previously regarded as the gold standard for diagnosing EP. TVU is currently considered to be the gold standard, with the ability to provide high quality examinations and high preoperative diagnosis rates [23,24]. Currently, the popularity of minimally invasive methods in all branches of surgery is increasing. We therefore recommend attempting expectant management or MTX treatment instead of surgery in haemodynamically stable patients without severe pain, albeit clinically suspicion of rupture.

The selection criteria for the expectant treatment option were suggested by the American College of Obstetricians and Gynecologists (ACOG) for patients who do not have a gestational sac or any suspicious extra-uterine masses viewable on ultrasonography, who have low β-HCG levels (<200 mIU/mL) and in whom decreasing β-HCG levels are observed [4]. In our study, we found that the initial β-HCG levels of the patients who received expectant treatment was an average of 626±443 mIU/mL, and the rate of success was 81%. In a literature review, the success rate of expectant management ranged between 47% and 73% in large patient series. However, this rate increased to 92-100% if the cases included small numbered patient series [25-28]. A multicenter, randomized study by Van Mello et al., reported that an expectant management group with an average initial β-HCG level of 708 mIU/mL had similar success rates to a single dose MTX treatment group with an average initial β-HCG level of 535 mIU/mL. The authors concluded that systemic MTX treatment was not superior to expectant management for patients who had visible EP and low β-HCG levels (1500 mIU/mL) or whose b-HCG levels plateaued (<2000 mIU/mL) for unknown reasons. In the same study, surgical treatment was needed in 13% of cases of expectant management and 2% of cases receiving a single dose of MTX treatment, among patients who had abdominal pain during the subsequent week [29]. In contrast, we found that the rate of the need for surgical treatment was 5% in the expectant management group and 11% in the medical treatment group. We could not find any significant differences ultrasonographically between the patients who needed surgical treatment and the patients that did not require surgical intervention. We concluded that the decreased surgery rate in the expectant management group and the increased surgery rate in the medical treatment group might be due to the differences in initial β-HCG levels.

Kirk et al., compared expectant management and MTX treatment by measuring the b-HCG levels before treatment and at 48 hours in 81 cases of tubal EP. They provided expectant management to patients whose β-HCG ratio of the 48th hour level to the 0th

hour level was less than 1. They reported that 39 patients were followed with expectant management and 42 patients underwent medical treatment. Their success rates were similar, at 72% and 76%, respectively [30].

In a double blind, placebo-controlled clinical trial, Silva et al., compared MTX treatment with placebo saline. MTX was administered in 10 cases of tubal EP with initial β-HCG levels of 883+729 mIU/mL and placebo saline was administered in 13 cases of tubal EP with initial β-HCG levels of 794±868 mIU/mL. There was no statistically significant difference between groups. The authors remarked that expectant management was less costly and prevented unnecessarily specific treatments [31].

In the literature, a small number of studies have reported the management of EP in women with initial free peritoneal fluid. Free peritoneal fluid is accepted to be a predictor factor for MTX treatment failure [9,20,32]. In a pilot study by Bignardi et al., including 8 cases of EP in women with free abdominal fluid on ultrasound examination, they reported a success rate of 75% (6/8) and failure rate of 25% (2/8) among patients who were managed expectantly [33], and they reported a failure rate of 25% (2/8) when MTX was administered. They concluded that the finding of free abdominal fluid on ultrasound examination might not be an absolute contraindication for conservative management of tubal EP.

Gnisci et al., reported successful MTX treatment in 69 of 93 extra-uterine pregnancies. They observed a mean of 7±12 mm of free abdominal fluid in the patients who were treated with MTX successfully (17/69) and a mean of 15.8±18 mm of fluid in the patients whose MTX treatment ended in failure (15/24). Furthermore, they found that the MTX failure group had higher initial serum β-HCG levels (1584/2545) and a higher haemoperitoneum rate (24.6%/62.5%). They remarked that the presence of initial free fluid was a more important predictor of MTX treatment failure than increased β-HCG levels, the presence of a gestational sac or the diameter of the adnexal mass [32].

Krissi et al., studied 102 EP for which a single dose of MTX treatment was administered. In their study, the rate of the presence of free peritoneal fluid was 56.6% (43/76) in patients in whom the initial dose of MTX was successful and 65.4% (17/26) in patients who required a second dose of MTX. Free peritoneal fluid was detected in 55.4% (51/92) of the patients who were treated successfully with a single or second dose of MTX. Free peritoneal fluid was detected significantly more in patients (90%, 9/10) whose medical treatment was unsuccessful after the single or second dose of MTX and who required surgical operations [34].

Lui et al., compared MTX treatment and expectant management in 35 women with EP who were haemodynamically stable, were diagnosed with a <3 cm ectopic gestation, had <100 ml of free pelvic fluid and had no fetal cardiac activity [35]. They reported a success rate of 100% (17/17) in the expectant management group and a success rate of 89% (16/18) in the MTX treatment group.

We included patients with peritoneal free fluid greater than 3 cm in the deepest pouch of Douglas on TVU. We reported that our success rate with single dose MTX was 76%, with both single or second dose MTX, it was 88%, and with expectant management, it was 81% despite the higher free abdominal fluid measurements, compared to Gnisci et al., Krissi et al., and Lui et al., [32,34,35].

We believe that the literature includes fewer articles about expectant management and initial free peritoneal fluid because the small amount of free peritoneal fluid can go unnoticed during examination. It might not always be possible to detect free intraperitoneal fluid, or it might not be possible to determine the amount of free intraperitoneal fluid directly. The detectable minimum amount of peritoneal fluid has been investigated in some studies. The outcomes have shown that peritoneal fluid volume could be detected at an approximate level of 620 to 670 ml in Morrison's pouch and at 160 ml in the pelvis [36,37]. It has been indicated by some authors that small amounts of free peritoneal fluid (<400 ml) are more difficult to detect [38,39].

Several factors can affect the measurement of intraperitoneal fluid. Free intraperitoneal fluid disperses into the deep parts of the peritoneum, such as the rectovesicular, rectouterine and hepatorenal spaces, in the supine position due to gravity. Sources of blood loss, blood clots, gas patterns, adhesions and patient position are variable factors in determining the location of the free peritoneal fluid.

LIMITATION

The retrospective nature of our study has limitations compared with prospective trials; however, every effort was made to provide high quality and long-termed unbiased data.

CONCLUSION

In conclusion, expectant management or MTX treatment should be the first line treatment for EP patients with initial free intraperitoneal fluid who are haemodynamically stable based on their β-HCG level follow-ups. For these patients, the presence of initial intraperitoneal fluid should not be considered as a negative predictor of treatment failure. Minimally invasive attempts should be taken into account due to their cost-effectiveness, short hospitalization times and decreased morbidity.

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