

Tubal ectopic pregnancy: our experience from 2000 to 2013

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Summary. In this paper we summarize our experience in diagnosis and treatment of 402 retrospectively collected tubal EP and review the most recent topics from the literature. Systemic Methotrexate (MTX) was effective in 56 out of 65 patients (failure rate 13.8%), in whom hCG level was significantly lower when compared to the failure group ($p < 0,05$); we performed 299 salpingectomies, 297 of whom through laparoscopic approach. MTX single-dose is safe and effective in eligible patients; surgery represents the treatment of most of the EPs, mainly through laparoscopic approach. (www.actabiomedica.it)

Key words: ectopic pregnancy, tubal pregnancy, Methotrexate, salpingectomy, laparoscopic salpingectomy

Introduction

Ectopic pregnancy (EP) occurs when fertilized ovum is implanted outside the endometrial cavity. The fallopian tube is the most common location for an EP. As summarized in table 1, other implantation sites may be the ovary, cervix, abdomen, cesarean scars (CSP) and uterine cornua (interstitial pregnancy) (1).

EP rate in industrialized countries has considerably increased over the last few decades (2) partly be-

cause of an increased incidence, due to the increased incidence of pelvic inflammatory disease (PID) (3), partly because of the improved diagnostic accuracy of the disease. Nowadays EP accounts for the 2.6% of all pregnancies (4), affects mainly patients aged between 35 and 44 years and accounts for the 16% of vaginal bleeding and pelvic pain in the first trimester of pregnancy (5).

A number of risk factors, such as prior ectopic pregnancy (EP), obstructive tubal disease as a consequence of PID, previous tubal sparing surgery or endometriosis and congenital tubal obstructions have been associated with the development of tubal ectopic pregnancy (4, 6).

The aim of tubal EP treatment is to preserve patient's health and invariably ends with the termination of pregnancy (5). Medical and surgical approaches are available for tubal EP treatment: nowadays Methotrexate (MTX) and laparoscopic salpingectomy or salpingostomy are respectively the most commonly used medical and surgical options. The aim of this paper is to summarize our experience in diagnosis and treatment of tubal EP and review the most recent topics from the literature.

Table 1. Ectopic pregnancy (EP) location and incidence (7, 8)

Location	Frequency
Tubal EP	>90% 70% ampullary 12% isthmic 11,1% fimbrial
Interstitial EP	2,4%
Cornual EP	0,27%
Abdominal EP	1,3%
Ovarian EP	3%
Isthmic EP, Cervical EP	<1%
Cesarean scar pregnancy (CSP)	6% if prior cesarean delivery

Materials and methods

We retrospectively collected all cases of tubal EP treated at the University Hospital of Parma from 2000 and 2013. For each patient we recorded data regarding sociodemographical characteristics sexual, gynaecologic, reproductive histories, condition of conception, clinical symptoms (which are summarized in Table 3), hCG levels, features and location of the EP, treatment and length of hospital stay for patients which underwent surgical treatment.

Transvaginal ultrasound associated with serum beta-hCG essay represent the diagnostic gold standard approach for tubal EP (5). Ultrasonography provided information concerning the location and the diameter of the EP, tubal ring diameter, the presence or absence of yolk sac and embryo, embryonic hearth activity and pelvic free fluid.

Treatment options were medical or surgical. Non-symptomathic/paucisymptomathic and haemodinamically stable patients underwent medical treatment with MTX after adequate counselling. Eligibility criteria for MTX single-dose treatment were previously described in our paper (2) and were the absence of embryonic hearth activity, a gestational sac diameter shorter than 40 mm, beta-hCG level below 5000 mUI/mL, hCG level rise less than 50% 48 hours apart from the previous dosage, normal blood tests, normal liver and renal function, pelvic free fluid less than 100 mL. When

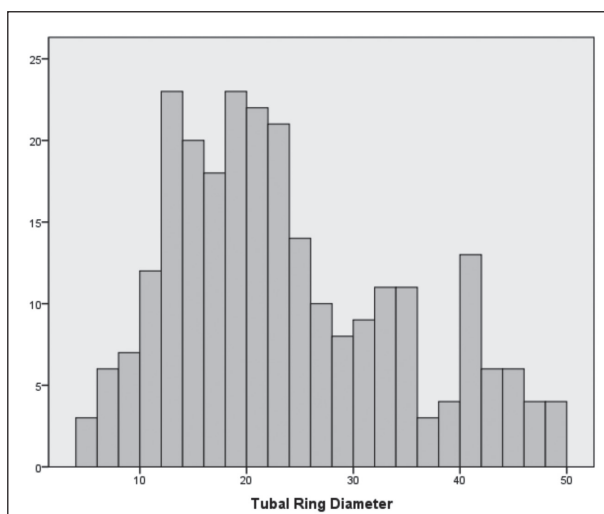


Figure 1. Tubal ring diameter

medical treatment with MTX failed all the patients underwent laparoscopic salpingectomy.

For statistical analysis we used IBM SPSS STATISTICS VERS. 20 package. For continuous variables we calculated mean and median value and standard deviation; quantitative data analysis regarded Pearson and Spearman tests; mean and median values were compared with Kruskal-Wallis test.

Results

402 patients were admitted with a tubal EP diagnosis between January 1st, 2000 and December 31st, 2013; the mean age was $32,48 \pm 5,59$ years; 341 (84,8%) of the patients included were Caucasian, 35 African (8,7%), 7 Asiatic (1,7%), 19 Caribbean (4,7%). Table 2 summarizes the reproductive history of the 402 patients included in the study.

Only 1 patient had a history of 3 previous tubal EP: she previously underwent bilateral salpingostomy and one tubal abortion, and after the fourth tubal EP underwent laparoscopic bilateral salpingectomy.

Data regarding clinical symptoms are summarized in Table 3. We didn't record the data concerning the presence or absence of pelvic free fluid because it is invariably associated with tubal EP, as reported by Stein et al (9).

Table 2. Obstetric and reproductive history of the patients included

		Number	Percentage	Total
Parity	Nulliparae	226	56,3%	402
	Uniparae	123	30,5%	
	Pluriparae	53	13,2%	
Previous extrauterine pregnancies	None	370	92%	402
	1	27	6,7%	
	2	4	1%	
	3	1	0,3%	
Conception	Spontaneous	395	98,2%	402
	IVF	7	1,8%	
Previous cesarean section	1	58	80,6%	72
	2	11	15,3%	
	3	3	4,2%	

Table 3. Clinical symptoms

	Yes	No	Total
Spontaneous pain	322 (80,1%)	80 (19,9%)	402
Evocated pain	195 (48,5%)	207 (51,5%)	402
Haemoperitoneum	182 (45,3%)	220 (54,7%)	402
Vaginal bleeding	227 (56,5%)	175 (43,5%)	402

38 patients (9,4%) were treated with attendance and had mean hCG levels of $850,59 \pm 818,614$ mUI/mL, median value of 671,5 mUI/mL, 95% CI 555,44 mUI/mL - 1145,73 mUI/mL.

Surgical procedures were 308: 299 patients underwent primary salpingectomy (176 right salpingectomies, 123 left salpingectomies), 9 patients underwent salpingectomy after medical treatment failure; laparotomic approach was necessary in 2 patients. The mean duration of hospitalization in surgically treated patients was $3,27 \pm 1,477$ days, median 3 days, 95% CI 3,08 - 3,45 days. We recorded 5 cases of post-surgical haemoperitoneum, which was treated laparoscopically.

Discussion

EP carries a risk of maternal death which is 10 times greater than that provided by term delivery (5). Nowadays 6% of maternal deaths during early pregnancy are a consequence of EP (4).

Sensitive β -hCG detection assays and improvement in imaging techniques allow early diagnosis and therefore a reduction in EP-related complications (4) and a wider range of treatment options.

Treatment options for tubal EP comprise conservative medical or surgical treatment or radical surgery with salpingectomy. Over the past 40 years medical treatment with MTX has been widely developed and in the meantime laparoscopy has emerged as the criterion standard technique for the surgical management of EP. Whatever the treatment, in addition to its effectiveness, the current issue is the preservation of patients' fertility, including limiting the risk of recurrence. The role of

treatment in optimizing subsequent fertility is a controversial subject, which has not been settled by previous studies and therefore is still subject to debate (10).

The most recent development in the medical treatment of ectopic pregnancy is the use of agents such as MTX, potassium chloride, hyperosmolar glucose, dactinomycin, prostaglandins, and mifepristone. MTX, a folic acid antagonist with antiproliferative activity that acts targeting and inhibiting the proliferation of rapidly dividing cells of gestational trophoblastic neoplasia represents the cornerstone of tubal EP medical treatment (5). Protocols involving a single dose of MTX have generally replaced older protocols in which women received three or more doses of MTX, usually alternating with leucovorin as rescue therapy (11). Stovall et al. described a single-dose protocol with a single administration of MTX 50 mg/m² in muscle (i.m.), which allows an outpatient management; according to Stovall et al. protocol a further administration of MTX 50 mg i.m. is necessary if hCG level doesn't reduce more than 15% between day 4 and day 7 (12). Systemic MTX has been considered for many years a safe and effective treatment for ectopic pregnancy, with a higher likelihood of success by lowering quantitative β -hCG, which represents the main prognostic factor, as demonstrated by Elito et al (13).

hCG cut-off value for MTX treatment has not been determined so far (6), and other factors such as tubal ring diameter and embryonic hearth activity have been proposed as predictors of medical treatment effectiveness. Elito et al and Stock et al (13, 14) reported MTX success in most of the patients with hCG levels less than 1500 mUI/ml; other Authors think that EP diameter <35 mm and the absence of embryonic hearth activity and bleeding could predict a successful medical treatment. It is important to keep in mind that MTX success does not preclude tubal rupture.

In our patients single-dose MTX was effective in 56 (13,9%) on 65 cases and failed in 9 patients (failure rate 13,8%); among these latter, 3 patients underwent emergent laparoscopy because of tubal rupture with haemoperitoneum (4,6%). In the remaining 6 patients we decided not to administer rescue dose and to perform laparoscopic salpingectomy. The initial serum chorionic gonadotropin concentration is the best prognostic indicator for treatment success in women

with ectopic pregnancies who are treated according to a single dose MTX protocol. Kruskal-Wallis test demonstrated a significant difference in quantitative hCG between patients successfully treated with MTX (mean value $2282,77 \pm 2005,43$ mUI/mL, median value 1711 mUI/mL, 95% CI 1706,74 - 2858,80) and patients in whom MTX failed (mean value $6177,37 \pm 5421$ mUI/mL, median value 5073 mUI/mL, 95% CI 2299,41 - 10055,34) ($p < 0,05$). 7 of the 9 patients in whom MTX failed had hCG levels above 5000 mUI/mL and refused primary laparoscopic approach.

Although the size of an ectopic gestational mass is frequently used as an exclusion criterion for MTX therapy, few data are available about the effect of this factor on success rates, therefore as reported by Limpscomb et al. (15). Some Authors consider the presence of pelvic free fluid at MTX administration a contraindication for medical treatment, whereas others reported that 50-62% of patients with pelvic free fluid had an unscathed salpinx (13, 15). Among the 56 patients successfully treated with single-dose MTX, 2 had hCG level < 5000 mUI/mL on day 0, whereas tubal ring diameter was < 35 mm in 40 of 47 cases available. Kruskal-Wallis test found no significant difference regarding tubal ring diameter between the patients successfully treated and the patients in whom MTX failed. Because of MTX antiproliferative effect, some Authors tested its effects on residual ovarian function: UYAR et al. demonstrated that MTX treatment does not reduce ovarian reserve in terms of antral follicle count (AFC) and antimullerian hormone levels (AMH). McLaren et al (16) and Oriol et al (17) found similar results. Beall et al demonstrated that MTX does not affect ovarian performance during ovarian stimulation protocols (18).

Beginning in the late 1970s laparoscopy has been used for patients with unruptured tubal EP (5) and now represents the gold standard surgical treatment of EP (19). Laparoscopy is the surgical procedure of choice to both confirm and remove an ectopic pregnancy, because it results in a shorter hospital stay and it usually allows a less lengthy convalescence when all hospital charges are analyzed, and therefore cost effectiveness favors laparoscopy over laparotomy (20). Laparotomy continues to play a role in exigent circumstances, such as hemodynamically unstable patients, shock, adhesions, and obesity (5). Juneau et al demonstrated that

laparoscopy and laparotomy do not differ in terms of recurrent EP and intrauterine pregnancy (6).

The most used surgical options are salpingectomy and salpingostomy. Salpingostomy is a procedure proposed in case of unscathed salpinx. The success rate of salpingectomy versus salpingostomy has not been studied in Randomized Controlled Trials (RCTs) so far and is still subject to debate (20). Salpingostomy seems to be affected by a higher persistent trophoblast rate (21) and a higher failure rate when compared to salpingectomy, and Authors proposed adjuvant treatment with MTX single-dose after salpingostomy (20, 22). Stock et al concluded that the only salpingostomy success predictor is a preoperative hCG value < 8000 mUI/mL (14); Kayatas et al reported salpingostomy failure in case of tubal ring diameter $> 33,5$ mm and fimbrial EP (19); other Authors suggested that salpingostomy may not be the elective approach in patients with a) uncontrolled hemorrhage from the implantation site, b) recurrent EP, c) severe tubal damage, d) great dimensions of the EP and e) in patients who do not desire further pregnancies or are planning IVF (23). After considering hCG levels and tubal anatomic features we decided to perform salpingectomy in all 299 patients, 2 of these with laparotomic approach. We decided to perform salpingectomy because of the small risk of tubal bleeding in the immediate postoperative period, the potential need for further treatment for persistent trophoblast and the possibility of a repeat EP in the conserved tube, as reported in the ESEP study; moreover, salpingectomy is easier to perform and more quickly done than salpingostomy (24) and at present there is no evidence of differences in terms of fertility and pregnancy rate between the two surgical procedures.

Even with the significant advances of laparoscopy and MTX, expectant management has been advocated for selected patients with EP, as well as in patients with a diagnosis of pregnancy of undetermined location (PUL). When transvaginal ultrasound demonstrates neither IUP nor extrauterine pregnancy and the serum hCG titer is < 1000 mIU/mL, 88% of women with suspected EP have spontaneous resolution with expectant management (5). A success rate of 76% is reported in selected patients, with a lower infertility likelihood when compared to salpingectomy. Inclusion criteria for expectant management have not been defined so

far, and patient need to undergo a strict clinical and biochemical follow-up. Expectant management was effective in 38 of the included patients (9,5%), in whom mean hCG level was $850,59 \pm 818,614$ mUI/mL and 95% CI 555,44-1145,73 mUI/mL; 7 of them had hCG levels above 1000 mUI/ml.

On the basis of our results we can conclude that MTX is an effective and safe option in selected and compliant patients, as well as expectant management. Nowadays surgery represents the treatment of most of the EP, mainly with laparoscopic approach, preferably with salpingectomy rather than salpingostomy.

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